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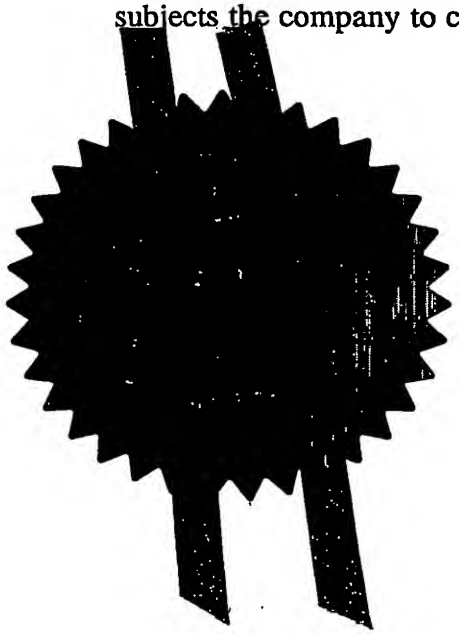

Signed A W Brewer

Dated 12 August 2003

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1/77

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Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

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1. Your reference — ARG/DAB/P33089

2. Patent application number
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01AUG02 E737606-1 D02029
P01/7700 0.00-0217757.4

0217757.4

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

~~SMITHKLINE BEECHAM CORPORATION~~
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~~Glaxo Wellcome House, Berkeley Avenue,~~
~~Greenford, Middlesex UB6 0NN, Great Britain~~

PO BOX 7929
ONE FRANKLIN PLAZA
PHILADELPHIA
PENNSYLVANIA
19101
UNITED STATES OF AMERICA

Patents ADP number *(if you know it)* 05966417004

If the applicant is a corporate body, give the country/state of its incorporation ~~United Kingdom~~ USA - PENNSYLVANIA

4. Title of the invention — Novel Compounds

5. Name of your agent *(if you have one)*

Corporate Intellectual Property

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

GlaxoSmithKline
Corporate Intellectual Property CN925.1
980 Great West Road
BRENTFORD
Middlesex TW8 9GS

Patents ADP number *(if you know it)* 79609820

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer yes if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is named as an applicant, or
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Patents Form 1/77

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Continuation sheets of this form	
Description	46
Claim(s)	3
Abstract	1
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10. If you are also filing any of the following, state how many against each item.

Priority Documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. We request the grant of a patent on the basis of this application

Signature A R Gladwin Date 30-Jul-02

12. Name and daytime telephone number of person to contact in the United Kingdom: A R Gladwin 01279 644934

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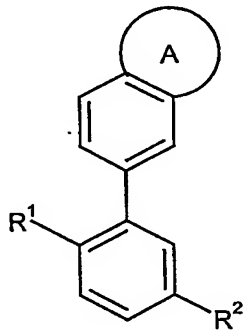
Novel Compounds

This invention relates to novel compounds and their use as pharmaceuticals, particularly as p38 kinase inhibitors, for the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

We have now found a group of novel compounds that are inhibitors of p38 kinase.

According to the invention there is provided a compound of formula (I):



(I)

wherein

A is a fused 5-membered heteroaryl ring optionally substituted by up to two substituents independently selected from C_{1-6}alkyl, -$(CH_2)_m$-C_{3-7}cycloalkyl, halogen, cyano, trifluoromethyl, -$(CH_2)_m$$OR^3$, -$(CH_2)_m$$NR^3R^4$, -$(CH_2)_m$$CONR^3R^4$, -$(CH_2)_m$$NHCOR^3$, -$(CH_2)_m$$SO_2NR^3R^4$, -$(CH_2)_m$$NHSO_2R^3$, -$(CH_2)_m$$SO_2(CH_2)_n$$R^5$, a 5- or 6-membered heterocyclyl ring containing nitrogen optionally substituted by C_{1-2}alkyl and a 5-membered heteroaryl ring optionally substituted by C_{1-2}alkyl;

R^1 is selected from methyl and chloro;

R^2 is selected from -NH-CO-R^6 and -CO-NH-$(CH_2)_q$-R^7;

R^3 is selected from hydrogen, C_{1-6}alkyl optionally substituted by up to two OH groups, -$(CH_2)_m$-C_{3-7}cycloalkyl, -$(CH_2)_m$phenyl optionally substituted by R^8 and/or R^9 and -$(CH_2)_m$heteroaryl optionally substituted by R^8 and/or R^9

R^4 is selected from hydrogen and C_{1-6}alkyl, or

R^3 and R^4, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

R^5 is selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, heteroaryl optionally substituted by R^8 and/or R^9, and phenyl optionally substituted by R^8 and/or R^9;

R^6 is selected from hydrogen, C_{1-6}alkyl, -$(CH_2)_q$-C_{3-7}cycloalkyl, trifluoromethyl, -$(CH_2)_r$heteroaryl optionally substituted by R^{11} and/or R^{12}, and -$(CH_2)_r$phenyl optionally substituted by R^{11} and/or R^{12};

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $CONHR^{13}$, phenyl optionally substituted by R^{11} and/or R^{12}, and heteroaryl optionally substituted by R^{11} and/or R^{12};

R^8 and R^9 are each independently selected from halogen, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, COR^{15} , CO_2R^{15}, and heteroaryl, or

R^8 and R^9 are linked to form a fused 5-membered heterocyclyl ring containing one heteroatom selected from oxygen, sulphur and N-R^{10};

R^{10} is selected from hydrogen and methyl;

R^{11} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, $-(CH_2)_q$-C_{3-7}cycloalkyl, $-CONR^{13}R^{14}$, $-NHCOR^{14}$, halogen, CN, $-(CH_2)_sNR^{16}R^{17}$, trifluoromethyl, phenyl optionally substituted by one or more R^{12} groups, and heteroaryl optionally substituted by one or more R^{12} groups;

R^{12} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, and $-(CH_2)_sNR^{16}R^{17}$;

R^{13} and R^{14} are each independently selected from hydrogen and C_{1-6}alkyl, or

R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10}, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^{15} is C_{1-6}alkyl;

R^{16} is selected from hydrogen, C_{1-6}alkyl and $-(CH_2)_q$-C_{3-7}cycloalkyl optionally substituted by C_{1-6}alkyl,

R^{17} is selected from hydrogen and C_{1-6}alkyl, or

R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

m is selected from 0, 1, 2 and 3;

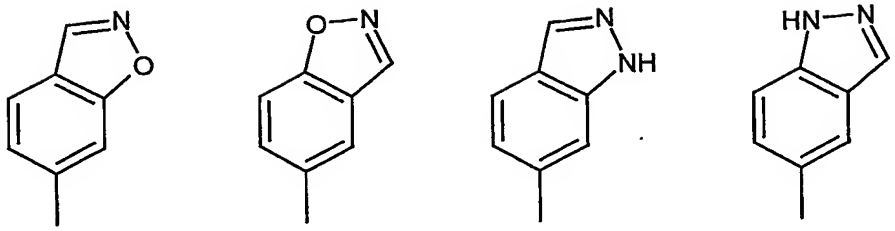
n is selected from 0, 1, 2 and 3;

q is selected from 0, 1 and 2;

r is selected from 0 and 1; and

s is selected from 0, 1, 2 and 3.

Representative examples of A include fused 5-membered heteroaryl rings containing up to two heteroatoms independently selected from oxygen, nitrogen and sulfur. Preferred fused 5-membered heteroaryl rings include rings containing up to two heteroatoms independently selected from oxygen and nitrogen, in particular rings containing two heteroatoms selected from oxygen and nitrogen such as rings containing a nitrogen atom and one additional heteroatom selected from oxygen and nitrogen. In one embodiment, A is selected from fused pyrazolyl and isoxazolyl rings such as those shown below:



Ring A may be optionally substituted by up to two substituents, located on any position on the ring. Typical substituents for A include C_{1-4}alkyl, in particular methyl, $-(CH_2)_mOR^3$, $-(CH_2)_mNR^3R^4$, $-(CH_2)_mSO_2(CH_2)_nR^5$, and a 5- or 6-membered heterocyclyl ring containing nitrogen, in particular piperazinyl and piperidinyl such as 4-piperidinyl.

A representative example of R^1 is methyl.

Representative examples of R^3 include hydrogen and C_{1-4}alkyl substituted by up to two OH groups, in particular 1,3-dihydroxyprop-2-yl.

A representative example of R^4 is hydrogen.

Representative examples of R^5 include C_{1-4}alkyl, in particular methyl, phenyl optionally substituted by R^8 and/or R^9, and a 5-membered heteroaryl ring containing at least one heteroatom selected from oxygen, nitrogen and sulphur optionally substituted by R^8 and/or R^9, in particular thienyl optionally substituted by R^8 and/or R^9.

Representative examples of R^6 include $-(CH_2)_r$heteroaryl optionally substituted by R^{11} and/or R^{12}, in particular in a 5- or 6-membered heteroaryl containing at least one heteroatom selected from oxygen, nitrogen and sulfur, for example, pyridinyl optionally substituted by $-(CH_2)_sNR^{16}R^{17}$, furyl or thienyl.

Representative examples of R^7 include C_{3-7}cycloalkyl, phenyl optionally substituted by R^{11} and/or R^{12}, and heteroaryl optionally substituted by R^{11} and/or R^{12}. In one embodiment, R^7 is selected from C_{3-6}cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl, in particular cyclopropyl; phenyl optionally substituted by C_{1-4}alkoxy, in particular methoxy; or $-(CH_2)_sNR^{16}R^{17}$; and heteroaryl optionally substituted by R^{11} and/or R^{12}, in particular a 5- or 6-membered heteroaryl containing at least one heteroatom selected from oxygen, nitrogen and sulfur, for example, thiazolyl or thiadiazolyl.

In one embodiment, R^8 and R^9 are each independently selected from halogen, in particular fluorine, cyano, trifluoromethyl, C_{1-4}alkoxy, in particular methoxy, COR^{15}, CO_2R^{15}, and heteroaryl, in particular a 5-membered heteroaryl ring containing up to two heteroatoms independently selected from nitrogen and oxygen, for example isoxazolyl. In another embodiment, R^8 and R^9 are linked to form a fused 5-membered heterocyclyl ring containing oxygen.

Representative examples of R^{11} and R^{12} include C_{1-4}alkoxy, in particular methoxy, and $-(CH_2)_sNR^{16}R^{17}$.

Representative examples of R^{15} include C_{1-4}alkyl, in particular methyl.

In one embodiment R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally further containing one additional oxygen atom, in particular pyrrolidinyl or morpholino.

In one embodiment, m is selected from 0, 1 and 2, in particular 0 and 1.

Representative examples of n include 0 and 1.

Representative examples of q include 0 and 1, in particular 0.

A representative example of r is 0.

A representative example of s is 0.

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Particular compounds according to the invention include those mentioned in the Examples.

As used herein, the term "alkyl" refers to straight or branched hydrocarbon chains containing the specified number of carbon atoms. For example, C_{1-6}alkyl means a straight or branched alkyl containing at least 1, and at most 6, carbon atoms. Examples of "alkyl" as used herein include, but are not limited to, methyl, ethyl, n-propyl, n-butyl, n-pentyl, isobutyl, isopropyl and t-butyl. A C_{1-4}alkyl group is preferred, for example methyl, ethyl, isopropyl or t-butyl. The said alkyl groups may be optionally substituted with one or more fluorine atoms for example, trifluoromethyl.

As used herein, the term "alkoxy" refers to a straight or branched chain alkoxy group, for example, methoxy, ethoxy, propoxy, prop-2-oxy, butoxy, but-2-oxy, 2-methylprop-1-oxy, 2-methylprop-2-oxy, pentoxy, or hexyloxy. A C_{1-4}alkoxy group is preferred, for example methoxy or ethoxy.

As used herein, the term "cycloalkyl" refers to a non-aromatic hydrocarbon ring containing the specified number of carbon atoms which may optionally contain up to one double bond. For example, C_{3-7}cycloalkyl means a non-aromatic ring containing at least three, and at most seven, ring carbon atoms. Examples of "cycloalkyl" as used herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl. A C_{3-6}cycloalkyl group is preferred, for example, cyclopropyl, cyclopentyl or cyclohexyl.

As used herein, the terms "heteroaryl ring" and "heteroaryl" refer to a monocyclic 5- to 7-membered unsaturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the heteroaryl ring has five or six ring atoms. Examples of heteroaryl rings include, but are not limited to, furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, triazolyl, tetrazolyl, thiadiazolyl, pyridyl, pyridazinyl, pyrimidinyl, pyrazinyl and triazinyl. The said ring may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl and oxy.

As used herein, the terms "heterocyclic ring" or "heterocyclyl" refer to a monocyclic 3- to 7-membered saturated hydrocarbon ring containing at least one heteroatom independently selected from oxygen, nitrogen and sulfur. Preferably, the

heterocyclyl ring has five or six ring atoms. Examples of heterocyclyl groups include, but are not limited to, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl, morpholino, tetrahydropyranyl, tetrahydrofuranyl, and thiomorpholino. The said ring may be optionally substituted by one or more substituents independently selected from C_{1-6}alkyl and oxy.

As used herein, the terms "halogen" or "halo" refer to the elements fluorine, chlorine, bromine and iodine. Preferred halogens are fluorine, chlorine and bromine. A particularly preferred halogen is fluorine or chlorine.

As used herein, the term "solvate" refers to a complex of variable stoichiometry formed by a solute (in this invention, a compound of formula (I) or a salt thereof) and a solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include water, methanol, ethanol and acetic acid. Preferably the solvent used is a pharmaceutically acceptable solvent. Examples of suitable pharmaceutically acceptable solvents include water, ethanol and acetic acid. All such solvates are included within the scope of the present invention.

Certain compounds of formula (I) may exist in stereoisomeric forms (e.g. they may contain one or more asymmetric carbon atoms or may exhibit cis-trans isomerism). The individual stereoisomers (enantiomers and diastereomers) and mixtures of these are included within the scope of the present invention. The present invention also covers the individual isomers of the compounds represented by formula (I) as mixtures with isomers thereof in which one or more chiral centres are inverted. Likewise, it is understood that compounds of formula (I) may exist in tautomeric forms other than that shown in the formula and these are also included within the scope of the present invention.

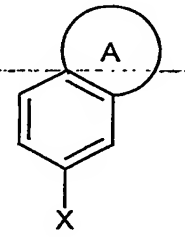
Salts of the compounds of the present invention are also encompassed within the scope of the invention and may, for example, comprise acid addition salts resulting from reaction of an acid with a basic nitrogen atom present in a compound of formula (I).

Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Representative salts include the following salts: Acetate, Benzenesulfonate, Benzoate, Bicarbonate, Bisulphate, Bitartrate, Borate, Bromide, Calcium Edetate, Camsylate, Carbonate, Chloride, Clavulanate, Citrate, Dihydrochloride, Edetate, Edisylate, Estolate, Esylate, Fumarate, Gluceptate, Gluconate, Glutamate, Glycollylarsanilate, Hexylresorcinate, Hydrabamine, Hydrobromide, Hydrochloride, Hydroxynaphthoate, Iodide, Isethionate, Lactate, Lactobionate, Laurate, Malate, Maleate, Mandelate, Mesylate, Methylbromide, Methylnitrate, Methylsulphate, Monopotassium Maleate, Mucate, Napsylate, Nitrate, N-methylglucamine, Oxalate, Pamoate (Embonate), Palmitate, Pantothenate, Phosphate/diphosphate, Polygalacturonate, Potassium, Salicylate, Sodium, Stearate, Subacetate, Succinate, Tannate, Tartrate, Teoclate, Tosylate, Triethiodide, Trimethylammonium and Valerate. Other salts which are not

pharmaceutically acceptable may be useful in the preparation of compounds of this invention and these form a further aspect of the invention.

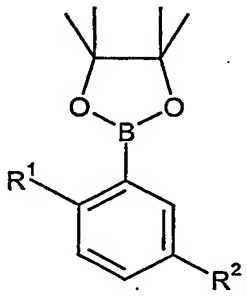
The compounds of this invention may be made by a variety of methods, including standard chemistry. Any previously defined variable will continue to have the previously defined meaning unless otherwise indicated. Illustrative general synthetic methods are set out below and then specific compounds of the invention are prepared in the working Examples.

A compound of formula (I) may be prepared by reacting a compound of formula (II)



(II)

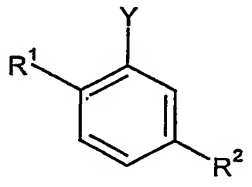
in which A is as hereinbefore defined and X is halogen, in particular bromine, with a compound of formula (III)



(III)

in which R^1 and R^2 are as hereinbefore defined,
in the presence of a catalyst, for example tetrakis(triphenylphosphine)palladium.

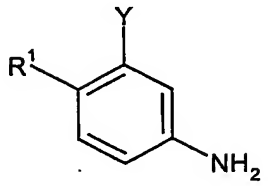
A compound of formula (III) may be prepared by, for example, reacting a compound of formula (IV)



(IV)

in which R^1 and R^2 are as hereinbefore defined and Y is halogen, in particular iodine, with bis(pinnacolato)diboron, [1,1'-bis(diphenylphosphino)ferrocene] dichloropalladium (II) complex ($PdCl_2$(ppdf)) and potassium acetate in a solvent such as DMF.

When R^2 is –NH-CO-R^6, a compound of formula (IV) may be prepared by reacting an amine of formula (V)



(V)

in which R^1 and Y are as hereinbefore defined,
with an acid compound of formula (VI)

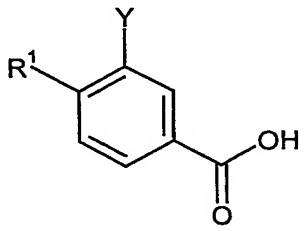
$$R^6CO_2H$$

(VI)

in which R^6 is as hereinbefore defined,
under amide forming conditions.

Suitable amide forming conditions are well known in the art and include adding a base such as DIPEA to a mixture of the amine of formula (V), the acid of formula (VI), and HATU in a solvent such as DMF.

Alternatively, when R^2 is –CO-NH-$(CH_2)_q$-R^7, a compound of formula (IV) may readily be prepared from a corresponding acid compound of formula (VII)



(VII)

in which R^1 and Y are as hereinbefore defined,
by converting the acid to an activated form of the acid, for example the acid chloride, by treatment with, for example, thionyl chloride, and then reacting the activated acid thus formed with an amine compound of formula (VIII)

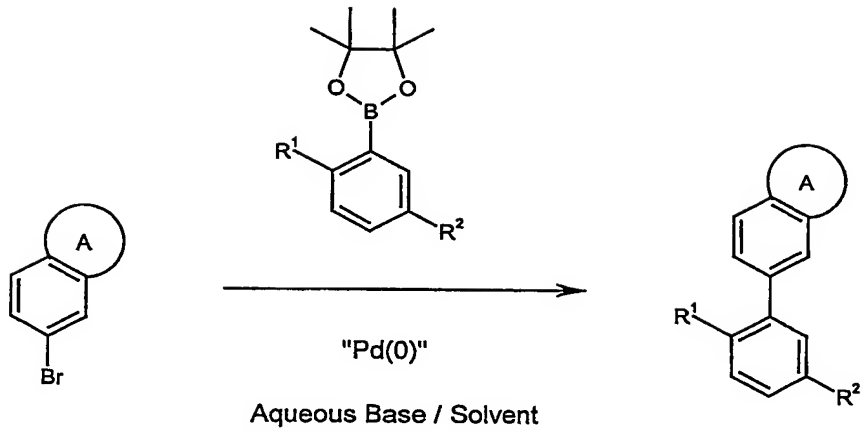
$$R^7\text{-}(CH_2)_q\text{-}NH_2$$

(VIII)

in which R^7 is as hereinbefore defined,
under amide forming conditions.

Suitable amide forming conditions are well known in the art and include treating a solution of the acid of formula (VII), or the activated form thereof, in for example DMF, with an amine of formula (VIII) in the presence of a base such as triethylamine.

For example, one general method for preparing the compounds of formula (I) comprises the reaction set out in Scheme 1 below.



Scheme 1

Alternatively, a further general method comprises final stage modification of one compound of formula (I) into another compound of formula (I). Suitable functional group transformations for converting one compound of formula (I) into another compound of formula (I) are well known in the art and are described in, for instance, *Comprehensive Heterocyclic Chemistry II*, eds. A. R. Katritzky, C. W. Rees and E. F. V. Scriven (Pergamon Press,1996), *Comprehensive Organic Functional Group Transformations*, eds. A.R. Katritzky, O. Meth-Cohn and C.W. Rees (Elsevier Science Ltd., Oxford, 1995), *Comprehensive Organic Chemistry*, eds. D. Barton and W.D. Ollis (Pergamon Press, Oxford, 1979), and *Comprehensive Organic Transformations*, R.C. Larock (VCH Publishers Inc., New York, 1989).

Whilst it is possible for the compounds of the present invention to be administered as the new chemical, the compounds of formula (I) are conveniently administered in the form of pharmaceutical compositions. Thus, in another aspect of the invention, we provide a pharmaceutical composition comprising a compound of formula (I), in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

The compounds of formula (I) may be formulated for administration in any suitable manner. They may, for example, be formulated for topical administration or administration by inhalation or, more preferably, for oral, transdermal or parenteral administration. The pharmaceutical composition may be in a form such that it can effect controlled release of the compounds of formula (I). A particularly preferred method of administration, and corresponding formulation, is oral administration.

For oral administration, the pharmaceutical composition may take the form of, and be administered as, for example, tablets (including sub-lingual tablets) and capsules (each including timed release and sustained release formulations), pills, powders, granules, elixirs, tinctures, emulsions, solutions, syrups or suspensions prepared by conventional means with acceptable excipients.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Powders are prepared by comminuting the compound to a suitable fine size and mixing with a

similarly comminuted pharmaceutical carrier such as an edible carbohydrate, as, for example, starch or mannitol. Flavoring, preservative, dispersing and coloring agent can also be present.

Capsules can be made by preparing a powder mixture as described above, and filling formed gelatin sheaths. Glidants and lubricants such as colloidal silica, talc, magnesium stearate, calcium stearate or solid polyethylene glycol can be added to the powder mixture before the filling operation. A disintegrating or solubilizing agent such as agar-agar, calcium carbonate or sodium carbonate can also be added to improve the availability of the medicament when the capsule is ingested.

Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like. Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like. Disintegrators include, without limitation, starch, methyl cellulose, agar, bentonite, xanthan gum and the like. Tablets are formulated, for example, by preparing a powder mixture, granulating or slugging, adding a lubricant and disintegrant and pressing into tablets. A powder mixture is prepared by mixing the compound, suitably comminuted, with a diluent or base as described above, and optionally, with a binder such as carboxymethylcellulose, an aliginate, gelatin, or polyvinyl pyrrolidone, a solution retardant such as paraffin, a resorption accelerator such as a quaternary salt and/or an absorption agent such as bentonite, kaolin or dicalcium phosphate. The powder mixture can be granulated by wetting with a binder such as syrup, starch paste, acadia mucilage or solutions of cellulosic or polymeric materials and forcing through a screen. As an alternative to granulating, the powder mixture can be run through the tablet machine and the result is imperfectly formed slugs broken into granules. The granules can be lubricated to prevent sticking to the tablet forming dies by means of the addition of stearic acid, a stearate salt, talc or mineral oil. The lubricated mixture is then compressed into tablets. The compounds of the present invention can also be combined with free flowing inert carrier and compressed into tablets directly without going through the granulating or slugging steps. A clear or opaque protective coating consisting of a sealing coat of shellac, a coating of sugar or polymeric material and a polish coating of wax can be provided. Dyestuffs can be added to these coatings to distinguish different unit dosages.

Oral fluids such as solution, syrups and elixirs can be prepared in dosage unit form so that a given quantity contains a predetermined amount of the compound. Syrups can be prepared by dissolving the compound in a suitably flavored aqueous solution, while elixirs are prepared through the use of a non-toxic alcoholic vehicle. Suspensions can be formulated by dispersing the compound in a non-toxic vehicle. Solubilizers and emulsifiers such as ethoxylated isostearyl alcohols and polyoxy

ethylene sorbitol ethers, preservatives, flavor additives such as peppermint oil or saccharin, and the like can also be added.

Where appropriate, dosage unit formulations for oral administration can be microencapsulated. The formulation can also be prepared to prolong or sustain the release as for example by coating or embedding particulate material in polymers, wax or the like.

The compounds of the present invention can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the present invention can also be administered in the form of liposome emulsion delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

Compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspartamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the compounds of the present invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels.

The present invention includes pharmaceutical compositions containing 0.1 to 99.5%, more particularly, 0.5 to 90% of a compound of the formula (I) in combination with a pharmaceutically acceptable carrier.

Likewise, the composition may also be administered in nasal, ophthalmic, otic, rectal, topical, intravenous (both bolus and infusion), intraperitoneal, intraarticular, subcutaneous or intramuscular, inhalation or insufflation form, all using forms well known to those of ordinary skill in the pharmaceutical arts.

For transdermal administration, the pharmaceutical composition may be given in the form of a transdermal patch, such as a transdermal iontophoretic patch.

For parenteral administration, the pharmaceutical composition may be given as an injection or a continuous infusion (e.g. intravenously, intravascularly or subcutaneously). The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. For administration by injection these may take the form of a unit dose presentation or as a multidose presentation preferably with an added preservative. Alternatively for parenteral administration the active ingredient may be in powder form for reconstitution with a suitable vehicle.

The compounds of the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

Alternatively the composition may be formulated for topical application, for example in the form of ointments, creams, lotions, eye ointments, eye drops, ear drops, mouthwash, impregnated dressings and sutures and aerosols, and may contain appropriate conventional additives, including, for example, preservatives, solvents to assist drug penetration, and emollients in ointments and creams. Such topical formulations may also contain compatible conventional carriers, for example cream or ointment bases, and ethanol or oleyl alcohol for lotions. Such carriers may constitute from about 1% to about 98% by weight of the formulation; more usually they will constitute up to about 80% by weight of the formulation.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebulizer, with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, tetrafluoroethane, heptafluoropropane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of e.g. gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of a compound of the invention and a suitable powder base such as lactose or starch.

The pharmaceutical compositions generally are administered in an amount effective for treatment or prophylaxis of a specific condition or conditions. Initial dosing in human is accompanied by clinical monitoring of symptoms, such symptoms for the selected condition. In general, the compositions are administered in an amount of active agent of at least about 100 μg/kg body weight. In most cases they will be administered in one or more doses in an amount not in excess of about 20 mg/kg body weight per day. Preferably, in most cases, dose is from about 100 μg/kg to about 5 mg/kg body weight, daily. For administration particularly to mammals, and particularly humans, it is expected that the daily dosage level of the active agent will be from 0. 1 mg/kg to 10 mg/kg and typically around 1 mg/kg. It will be appreciated that optimum dosage will be determined by standard methods for each treatment modality and indication, taking into account the indication, its severity, route of administration, complicating conditions and the like. The physician in any event will determine the actual dosage which will be most suitable for an individual and will vary with the age, weight and response of the particular individual. The effectiveness of a selected actual dose can readily be determined, for example, by measuring clinical symptoms or standard anti-inflammatory indicia after administration of the selected dose. The above dosages are exemplary of the average case. There can, of course, be individual instances where higher or lower

dosage ranges are merited, and such are within the scope of this invention. For conditions or disease states as are treated by the present invention, maintaining consistent daily levels in a subject over an extended period of time, e.g., in a maintenance regime, can be particularly beneficial.

In another aspect, the present invention provides a compound of formula (I) for use in therapy.

The compounds of the present invention are generally inhibitors of the serine/threonine kinase p38 and are therefore also inhibitors of cytokine production which is mediated by p38 kinase. Within the meaning of the term "inhibitors of the serine/threonine kinase p38" are included those compounds that interfere with the ability of p38 to transfer a phosphate group from ATP to a protein substrate according to the assay described below.

It is known that p38 kinase activity can be elevated (locally or throughout the body), p38 kinase can be incorrectly temporally active or expressed, p38 kinase can be expressed or active in an inappropriate location, p38 kinase can be constitutively expressed, or p38 kinase expression can be erratic; similarly, cytokine production mediated by p38 kinase activity can be occurring at inappropriate times, inappropriate locations, or it can occur at detrimentally high levels.

Accordingly, the present invention provides a method for the treatment of a condition or disease state mediated by p38 kinase activity, or mediated by cytokines produced by the activity of p38 kinase, in a subject which comprises administering to said subject a therapeutically effective amount of a compound of formula (I). The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention also provides a method of inhibiting cytokine production which is mediated by p38 kinase activity in a subject, e.g. a human, which comprises administering to said subject in need of cytokine production inhibition a therapeutic, or cytokine-inhibiting, amount of a compound of the present invention. The compound may be administered as a single or polymorphic crystalline form or forms, an amorphous form, a single enantiomer, a racemic mixture, a single stereoisomer, a mixture of stereoisomers, a single diastereoisomer or a mixture of diastereoisomers.

The present invention treats these conditions by providing a therapeutically effective amount of a compound of this invention. By "therapeutically effective amount" is meant a symptom-alleviating or symptom-reducing amount, a cytokine-reducing amount, a cytokine-inhibiting amount, a kinase-regulating amount and/or a kinase-inhibiting amount of a compound. Such amounts can be readily determined by standard methods, such as by measuring cytokine levels or observing alleviation of clinical symptoms. For example, the clinician can monitor accepted measurement scores for anti-inflammatory treatments.

The compounds of the present invention can be administered to any subject in need of inhibition or regulation of p38 kinase or in need of inhibition or regulation of

p38 mediated cytokine production. In particular, the compounds may be administered to mammals. Such mammals can include, for example, horses, cows, sheep, pigs, mice, dogs, cats, primates such as chimpanzees, gorillas, rhesus monkeys, and, most preferably, humans.

Thus, the present invention provides methods of treating or reducing symptoms in a human or animal subject suffering from, for example, rheumatoid arthritis, osteoarthritis, asthma, psoriasis, eczema, allergic rhinitis, allergic conjunctivitis, adult respiratory distress syndrome, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, silicosis, endotoxemia, toxic shock syndrome, inflammatory bowel disease, tuberculosis, atherosclerosis, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, epilepsy, multiple sclerosis, aneurism, stroke, irritable bowel syndrome, muscle degeneration, bone resorption diseases, osteoporosis, diabetes, reperfusion injury, graft vs. host reaction, allograft rejections, sepsis, systemic cachexia, cachexia secondary to infection or malignancy, cachexia secondary to aquired immune deficiency syndrome (AIDS), malaria, leprosy, infectious arthritis, leishmaniasis, Lyme disease, glomerulonephritis, gout, psoriatic arthritis, Reiter's syndrome, traumatic arthritis, rubella arthritis, Crohn's disease, ulcerative colitis, acute synovitis, gouty arthritis, spondylitis, and non articular inflammatory conditions, for example, herniated/ruptured/prolapsed intervertebral disk syndrome, bursitis, tendonitis, tenosynovitis, fibromyalgic syndrome and other inflammatory conditions associated with ligamentous sprain and regional musculoskeletal strain, pain, for example that associated with inflammation and/or trauma, osteopetrosis, restenosis, thrombosis, angiogenesis, cancer including breast cancer, colon cancer, lung cancer or prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease, epilepsy and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, psoriasis, chronic pulmonary inflammation, chronic obstructive pulmonary disease, chronic heart failure, systemic cachexia, glomerulonephritis, Crohn's disease and cancer including breast cancer, colon cancer, lung cancer and prostatic cancer, which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

A further aspect of the invention provides a method of treatment of a human or animal subject suffering from rheumatoid arthritis, asthma, chronic pulmonary

inflammation, chronic obstructive pulmonary disease, neurodegenerative disease, Alzheimer's disease, Parkinson's disease and epilepsy which comprises administering to said subject a therapeutically effective amount of a compound of formula (I).

The compounds of formula (I) may be employed alone or in combination with other therapeutic agents for the treatment of the above-mentioned conditions. In particular, in rheumatoid arthritis therapy, combination with other chemotherapeutic or antibody agents is envisaged. Combination therapies according to the present invention thus comprise the administration of at least one compound of formula (I) and at least one other pharmaceutically active agent. The compound(s) of formula (I) and the other pharmaceutically active agent(s) may be administered together or separately and, when administered separately, this may occur separately or sequentially in any order. The amounts of the compound(s) of formula (I) and the other pharmaceutically active agent(s) and the relative timings of administration will be selected in order to achieve the desired combined therapeutic effect. Examples of other pharmaceutically active agents which may be employed in combination with compounds of formula (I) for rheumatoid arthritis therapy include: immunosuppresants such as amtolmetin guacil, mizoribine and rimexolone; anti-TNFα agents such as etanercept, infliximab, diacerein; tyrosine kinase inhibitors such as leflunomide; kallikrein antagonists such as subreum; interleukin 11 agonists such as oprelvekin; interferon beta 1 agonists; hyaluronic acid agonists such as NRD-101 (Aventis); interleukin 1 receptor antagonists such as anakinra; CD8 antagonists such as amiprilose hydrochloride; beta amyloid precursor protein antagonists such as reumacon; matrix metalloprotease inhibitors such as cipemastat and other disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate, sulphasalazine, cyclosporin A, hydroxychoroquine, auranofin, aurothioglucose, gold sodium thiomalate and penicillamine.

Examples

The following Examples are illustrative embodiments of the invention, not limiting the scope of the invention in any way. Reagents are commercially available or are prepared according to procedures in the literature.

LCMS was conducted on a column (3.3cm x 4.6mm ID, 3um ABZ+PLUS), at a Flow Rate of 3ml/min, Injection Volume of 5µl, at room temperature and UV Detection Range at 215 to 330nm.

2-Chloroisonicotinic acid, 3-cyanobenzenesulfonyl chloride, 3,4-difluorobenzenesulfonyl chloride, 2,3-dihydro-1-benzofuran-5-sulfonyl chloride and 5-isoxazol-3-ylthiophene-2-sulfonyl chloride may be purchased from Maybridge Chemicals.

3-Iodo-4-methylaniline, 3-fluorobenzenesulfonyl chloride and 4-(trifluoromethyl)benzenesulfonyl chloride may be purchased from Avocado.

3-Methoxyphenylsulfonyl chloride may be purchased from Lancaster.

4-Acetylphenylsulfonyl chloride may be purchased from Acros.

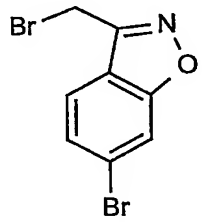
5-Bromoindazole may be prepared by the procedure described in Chem Ber, 1922, 55, 1141.

6-Bromo-3-piperidin-4-yl-1,2-benzisoxazole may be prepared by the procedure described in WO97/49698.

6-Bromo-3-methyl-1,2-benzisoxazole and 5-bromo-3-methyl-1,2-benzisoxazole may be prepared according to the procedures described in Indian J Chem Sect B, 1977, 15B, 1058-1063.

Methyl 4-[(chlorosulfonyl)methyl]benzoate may be prepared by the procedure described in Rec Trav Chim Pays-Bas, 1957, 76, 129.

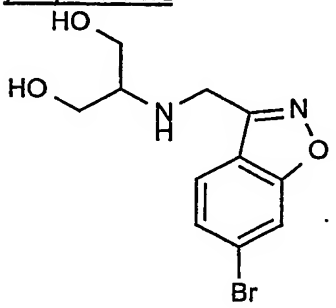
Intermediate 1: 6-Bromo-3-bromomethyl-1,2-benzisoxazole



A mixture of 6-bromo-3-methyl-1,2-benzisoxazole (675mg), N-bromosuccinimide (642mg) and 1,1'-azobis(cyclohexanecarbonitrile) (90mg) in carbon tetrachloride (7ml) was irradiated using a 300W lamp at reflux under nitrogen for 40h. On cooling the precipitate was removed by filtration, the solvent was evaporated and the residue was purified by flash chromatography on a silica column (4cm diam) eluting with a cyclohexane-ethyl acetate gradient (49:1 to 24:1) to give the title compound as a pale yellow solid (350mg).

LC-MS: Rt 3.67min.

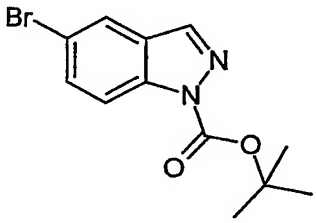
Intermediate 2: 2-[(6-Bromo-1,2-benzisoxazol-3-yl)methyl]amino-1,3-propanediol



A solution of 6-bromo-3-bromomethyl-1,2-benzisoxazole (Intermediate 1, 130mg), serinol (50mg) and DIPEA (0.05ml) in DMF (0.2ml) was stirred at 60° under nitrogen for 3h. The mixture was partitioned between water and ethyl acetate and the organic layer was washed with water and brine, dried through a hydrophobic filter and concentrated. The residue was purified on a Varian Bond Elut SPE cartridge (silica, 2g) eluting with dichloromethane followed by dichloromethane-methanol (9:1) to give the title compound as a yellow gum (33mg).

LC-MS: Rt 1.75min, MH+ 301,303.

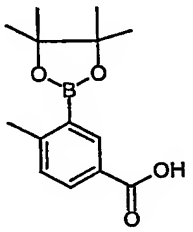
Intermediate 3: tert-Butyl 5-bromo-1H-indazole-1-carboxylate



A stirred ice-cold suspension of 5-bromoindazole (2g, 10.2mmol), 4-(dimethylamino)pyridine (250mg, 2.0mmol) and triethylamine (1.55ml, 11.2mmol) in acetonitrile (50ml) was treated with a solution of di-tert-butyl dicarbonate (2.8ml, 12.2mmol) in acetonitrile (20ml) over 15 min such that the temperature remained under 5°. The reaction mixture was warmed to room temp then stirred for 18h. The solvent was evaporated and the residue was purified by column chromatography on silica (100g) eluting with cyclohexane:ethyl acetate (15:1) to give the title compound (2.27g, 7.7mmol).

NMR: δH[$CDCl_3$] 8.10 (1H, s), 8.07 (1H, d), 7.86 (1H, d), 7.60 (1H, dd), 1.71 (9H, s).
LCMS: Rt 3.55min.

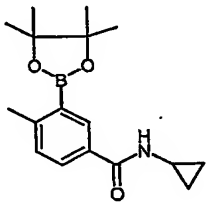
Intermediate 4: 4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)benzoic acid



3-Iodo-4-methylbenzoic acid (10g, 38.16mmol), bis(pinnacolato)diboron (14.5g, 57.24mmol), potassium acetate (18.73g, 190.8mmol) and $PdCl_2dppf$ (3.12g, 3.8mmol) in DMF (200ml) were heated at 80°C for 21hrs. The solvent was evaporated from the cooled reaction under vacuum, the residue dissolved in ethyl acetate (300ml) and hydrochloric acid (2N, 300ml) and filtered through celite. The organic phase was separated and the aqueous extracted with ethyl acetate (2 x 300ml). The combined organic extracts were washed with brine (500ml) and dried (magnesium sulphate). The solvent was evaporated under vacuum and the residue was absorbed onto silica and applied to a silica column. This was eluted with cyclohexane / ethyl acetate (5:1). to give the title compound.

NMR: δH [d6-DMSO] 12.83,(1H, b), 8.23,(1H, d), 7.89,(1H, dd), 7.29,(1H, d), 2.51,(3H, s), 1.30,(12H, s).
LCMS: Rt 3.65min.

Intermediate 5: *N*-Cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzamide

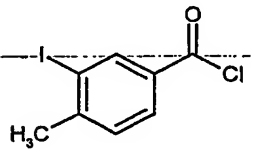


Intermediate 4 (10g) was dissolved in DMF (100ml). To this was added cyclopropylamine (2.2g) DIPEA (15ml) and HATU (14g). The mixture was stirred for 3 hours at room temp. The solvent was removed under vacuum and the residue was partitioned between ethyl acetate (400ml) and saturated sodium bicarbonate solution (400ml). The organic layer was dried over magnesium sulphate, filtered and concentrated under vacuum to give a pink solid. The product was purified using

Biotage chromatography on silica eluting with 50:50 ethylacetate/cyclohexane to give the title compound as a white solid.

NMR: δH [d6-DMSO] 8.42 (1H, d), 8.06 (1H, d), 7.77 (1H, dd), 7.23 (1H, d), 2.85 (1H, m), 2.47 (3H, s), 1.32 (12H, s), 0.67 (2H, m), 0.56 (2H, m).
LCMS: Rt 3.29min, MH^+ 302.

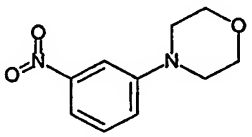
Intermediate 6: 3-Iodo-4-methylbenzoyl chloride



Thionyl chloride (8.2ml) was added to a mixture of 3-iodo-4-methylbenzoic acid (18.5g) in chloroform (100ml) and heated at 61°C for 16 hours. The solvent was removed under vacuum and excess thionyl chloride removed by azeotroping with toluene (3x30ml). The title compound was formed as a beige solid (19.5g) and used in subsequent reactions without further purification.

NMR: δH [d6-DMSO] 8.31 (1H, d), 7.87 (1H, dd), 7.46 (1H, d), 2.43 (3H, s).

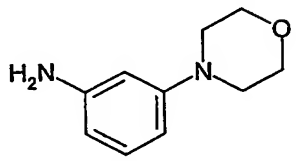
Intermediate 7: 4-(3-Nitrophenyl)morpholine



3-Fluoronitrobenzene (10g) was added to a solution of morpholine (34ml) in DMSO (120ml) and heated at 110°C for 60h. The reaction mixture was cooled and poured onto water (800ml). The precipitate was collected by filtration and the orange solid was dried under vacuum and used in subsequent reactions without further purification (13.7g).

NMR: δH [d6-DMSO] 7.68 (1H, dd), 7.62 (1H, dd), 7.49 (1H, t), 7.42 (1H, dd), 3.76 (4H, dd), 3.24 (4H, dd).

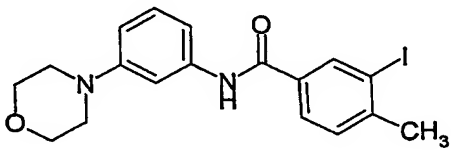
Intermediate 8: 3-(4-Morpholinyl)benzenamine



A flask containing 5% palladium on carbon (1.95g) was evacuated and refilled with hydrogen. 4-(3-Nitrophenyl)morpholine (Intermediate 7) (19.5g) was introduced into the flask as a solution in ethanol and DMF (1000ml, 4:1 v/v). The reaction was stirred at room temp until further uptake of hydrogen ceased (after approximately 7L). The reaction was then filtered through celite and solvent was removed under vacuum to give the title compound (12.6g) as a beige solid.

NMR: δH [d6-DMSO] 6.85 (1H, t), 6.12 (2H, m), 6.06 (1H, dd), 4.88 (2H, brs), 3.70 (4H, apparent t), 2.98 (4H, apparent t).
LCMS: Rt 1.08 min MH^+179.

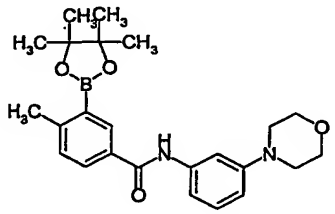
Intermediate 9: 3-Iodo-4-methyl-*N*-[3-(4-morpholinyl)phenyl]benzamide



3-Iodo-4-methylbenzoyl chloride (Intermediate 6) (19.5g) was added portion-wise to a mixture of triethylamine (48ml) and 3-(4-morpholinyl)benzenamine (Intermediate 8) (12.6g) in DMF (150ml) and the mixture was heated at 80°C for 16h. The solvent was removed under vacuum and the residue was dissolved in chloroform (200ml). The organic layer was washed with water (2x100ml), 2M sodium hydroxide solution (100ml) and brine (100ml), dried over magnesium sulphate, filtered and concentrated under vacuum The resulting yellow solid was triturated with diethyl ether and collected by filtration to yield the title compound as an off-white solid (20.0g). The product was used in subsequent reactions without further purification.

NMR: δH [d6-DMSO] 10.10 (1H,s), 8.39 (1H, d), 7.90 (1H, dd), 7.49 (1H, d), 7.38 (1H, t), 7.28 (1H, brd), 7.19 (1H, t), 6.71 (1H, dd), 3.75 (4H, apparent t), 3.10 (4H, apparent t), 2.44 (3H, s).
LCMS: Rt 3.52 min MH^+423.

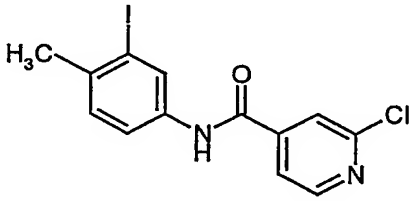
Intermediate 10: 4-Methyl-*N*-[3-(4-morpholinyl)phenyl]-3-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)benzamide



3-Iodo-4-methyl-*N*-[3-(4-morpholinyl)phenyl]benzamide (Intermediate 9) (8.00g) triethylamine (7.9ml) and bis(pinacolato)diboron (4.13ml) were added to a solution of $PdCl_2dppf$ (770mg) in dioxane (100ml) and the mixture was heated at 80° under nitrogen for 3h. The reaction was cooled, the solvent was removed under vacuum and the residue was dissolved in dichloromethane (150ml). The solution was washed with water (100mlx3) and brine (100ml) dried (magnesium sulphate) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica eluting with 30% ethyl acetate/cyclohexane to 50% ethyl acetate/cyclohexane to give the title compound as a white solid (4.05g).

NMR: δH [d6-DMSO] 10.11 (1H,s), 8.19 (1H, d), 7.93 (1H, dd), 7.40 (1H, brs), 7.33 (1H, d), 7.28 (1H, brd), 7.19 (1H, t), 6.70 (1H, dd), 3.75 (4H, apparent t), 3.09 (4H, apparent t), 2.54 (3H, s), 1.33 (12H, s).
LCMS: Rt 3.65 min MH^+423.

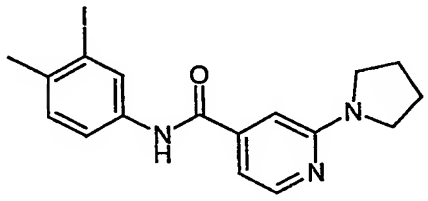
Intermediate 11: 2-Chloro-N-(3-iodo-4-methylphenyl)-isonicotinamide



2-Chloroisonicotinic acid (3.3g) HATU (8.75g) DIPEA (10.9ml) and 3-iodo-4-methylaniline (5.00g) in DMF (50ml) were heated under nitrogen for 16h. The reaction was cooled, the solvent was removed under vacuum and the residue was dissolved in dichloromethane (150ml). The solution was washed with water (3x100ml) and brine (100ml) dried (magnesium sulphate) and the solvent was removed under vacuum. The residue was purified by column chromatography on silica eluting with ethyl acetate/cyclohexane (40:60) to give the title compound as a white solid (7.00g).

NMR: δH [d6- DMSO] 10.52 (1H, s), 8.62 (1H, d), 8.29 (1H, d), 7.99 (1H, b), 7.87 (1H, dd), 7.70 (1H, dd), 7.34 (1H, d), 2.36 (3H, s).
LCMS: Rt 3.59 min MH^+373.

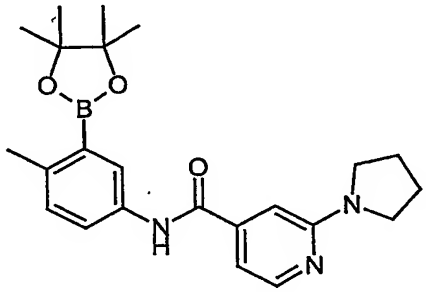
Intermediate 12: N-(3-Iodo-4-methylphenyl)-2-pyrrolidin-1-yl-isonicotinamide



A solution of N-(3-iodo-4-methylphenyl)-2-chloro-isonicotinamide (Intermediate 11) (7.00g) in pyrrolidine (20ml) was heated at 80°C under nitrogen for 16h. Excess pyrrolidine was removed under vacuum and the residue was triturated with diethyl ether (20ml). The resulting solid was collected by filtration and dried under vacuum to give the title compound as a pale yellow solid (7.73g).

NMR: δH [d6–DMSO] 10.29 (1H, s), 8.29 (1H, d), 8.20 (1H, d), 7.71 (1H, dd), 7.72 (1H, dd), 6.97 (1H, brd), 6.88 (1H, b), 3.45 (2H, apparent t), 3.09 (2H, m), 2.35 (3H, s), 1.98 (2H, m), 1.82 (2H, m).
LCMS: Rt 2.77 min MH^+408.

Intermediate 13: *N*-[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]-dioxaborolan-2-yl)phenyl]-2-(1-pyrrolidinyl)-4-pyridinecarboxamide

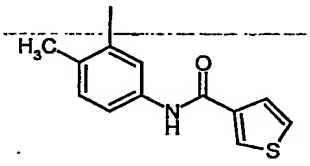


Bis(pinacolato)diborane (7.24g) was added to a mixture of N-(3-iodo-4-methylphenyl)-2-pyrrolidin-1-yl-isonicotinamide (Intermediate 12) (7.73g) potassium acetate (9.32g, 95mmol) and $PdCl_2dppf$ (770mg) in DMF (100ml and the reaction was heated at 80° under nitrogen for 16h. The reaction was cooled and the solvent was removed under vacuum. The residue was dissolved in chloroform (150ml), washed with water (3x100ml) and brine (100ml), dried (magnesium sulphate) and the solvent

was removed under vacuum. The residue was purified by column chromatography on silica eluting with ethyl acetate:cyclohexane (1:4) to (1:1) to give the title compound as a white solid (1.5g).

NMR: δH ($CDCl_3$) 8.27 (1H, d), 7.99 (1H, dd), 7.76 (1H, b), 7.65 (1H, d), 6.20 (1H, d), 6.82 (1H, b), 6.77 (1H, b), 3.52 (4H, apparent t), 2.52 (3H, s), 2.25 (4H, m), 1.35 (12H, s).
LCMS: Rt 2.90 min MH^+408.

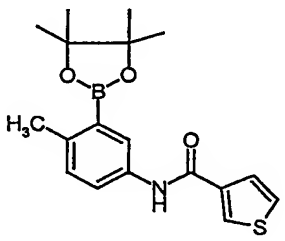
Intermediate 14: N-(3-Iodo-4-methylphenyl)thiophene-3-amide



Thiophene-3-carboxylic acid (2.75g) and HATU (8.15g) in DMF (25ml) were stirred at room temp for 15min. HOBT (2.9g), 3-iodo-4-methylaniline (5.0g) and DIPEA (11.2ml, 64.35mmol) were added and the reaction was stirred at room temp for 16h. The solvent was evaporated under vacuum and the residue was partitioned between ethyl acetate (100ml) and aqueous sodium carbonate (10%, 100ml). The aqueous layer was extracted with ethyl acetate (50ml) and the combined organic phases washed with hydrochloric acid (2N, 75ml), water (75ml) and brine (75ml). The organic phase was dried (magnesium sulphate) and absorbed onto silica. The silica was applied to a silica column and eluted with cyclohexane/ethyl acetate (4:1). The solvent was evaporated from the product fractions under vacuum to the title compound.

NMR: δH [d6-DMSO] 10.06,(1H, b), 8.34,(1H, m), 8.29,(1H, d), 7.70,(1H, dd), 7.66,(1H, dd), 7.62,(1H, dd), 7.30,(1H, d), 2.34,(3H, s).
LCMS: Rt 3.69min, MH^+ 344.

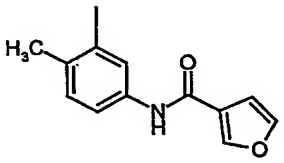
Intermediate 15: N-[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]thiophene-3-amide



N-(3-Iodo-4-methylphenyl)thiophene-3-amide (Intermediate 14) (2.64g) bis(pinnacolato)diboron (2.13g), potassium acetate (825mg) and $PdCl_2dppf$ (312mg) in DMF (20ml) were heated at 80°C for 20h. The cooled reaction was absorbed onto silica and applied to a Varian Bond-Elut SPE cartridge (silica, 10g) and eluted with a cyclohexane/ethyl acetate gradient. The product fractions were concentrated under vacuum to give the title compound.

NMR: δH [d6-DMSO] 9.99,(1H, b), 8.35,(1H, s), 7.90,(1H, d), 7.85,(1H, dd), 7.63,(2H, m), 7.14,(1H, d), 2.42,(3H, s), 1.30,(12H, s).
LCMS: Rt 3.65min, MH^+ 344.

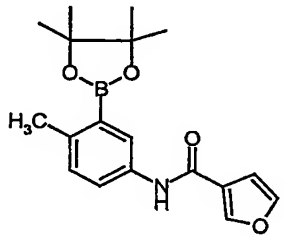
Intermediate 16: N-(3-Iodo-4-methylphenyl)-3-furamide



3-Furoic acid (2.4g) and HATU (8.15g) in DMF (25ml) were stirred at room temperature for 15min. HOBT (2.9g), 3-iodo-4-methylaniline (5.0g) and DIPEA (11.2ml) were added and the mixture was stirred at room temp for 16h. The solvent was evaporated under vacuum and the residue was partitioned between ethyl acetate (100ml) and aqueous sodium carbonate (10%, 100ml). The aqueous layer was extracted with ethyl acetate (50ml) and the combined organic phases were washed with hydrochloric acid (2N, 75ml), water (75ml) and brine (75ml). The organic phase was dried (magnesium sulphate) and absorbed onto silica. The silica was applied to a silica column and eluted with cyclohexane/ethyl acetate (3:1) to give the title compound.

NMR: δH [d6-DMSO] 9.92,(1H, b), 8.36,(1H, d), 8.23,(1H, d), 7.80,(1H, t), 7.66,(1H, dd), 7.29,(1H, d), 6.98,(1H, d), 2.33,(3H, s).
LCMS: Rt 3.52min, MH^+ 328.

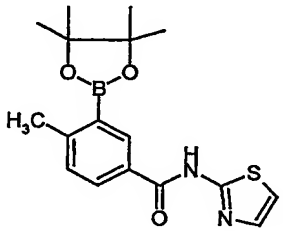
Intermediate 17: N-[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-furamide



N-(3-Iodo-4-methylphenyl)-3-furamide (Intermediate 16) (2.5g) bis(pinnacolato)diboron (2.13g) potassium acetate (825mg) and $PdCl_2dppf$ (312mg) in DMF (20ml) were heated at 80° for 20h. The cooled reaction was absorbed onto silica and applied to a Varian Bond-Elut SPE cartridge (silica, 10g) and eluted with a cyclohexane/ethyl acetate gradient. The product fractions were concentrated under vacuum to give the title compound.

NMR: δH [d6-DMSO] 9.86,(1H, b), 8.36,(1H, m), 7.86-7.82,(2H, m), 7.77,(1H, t), 7.14,(1H, d), 6.99,(1H, m), 2.41,(3H, s), 1.30,(12H, s).
LCMS: Rt 3.55min, MH^+ 328.

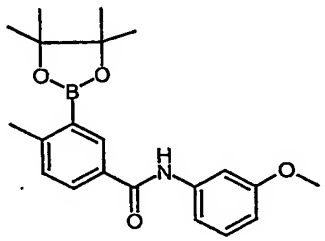
Intermediate 18: 4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(thiazol-2-yl)-benzamide



4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Intermediate 4) (2.0g) DIPEA (4ml) and HATU (3.05g) were dissolved in DMF (20ml) and stirred at room temp for 15min. 2-Aminothiazole (801mg) was added and the mixture was stirred at room temp for 18h. The solvent was evaporated under vacuum and the residue was partitioned between ethyl acetate (250ml) and water (50ml). The organic phase was washed with hydrochloric acid (2N, 50ml) and aqueous sodium bicarbonate (1M, 50ml) dried (magnesium sulphate) concentrated under vacuum. The residue was absorbed onto silica and purified by flash column chromatography eluting with cyclohexane/ethyl acetate (4:1) to give the title compound (1.72g).

NMR: δH [d6-DMSO] 12.65,(1H, b), 8.32,(1H, d), 8.08,(1H, dd), 7.56,(1H, d), 7.35,(1h, d), 7.28,(1H, d), 2.54,(3H, s), 1.34,(12H, s).
LCMS: Rt 3.66min, MH^+ 345.

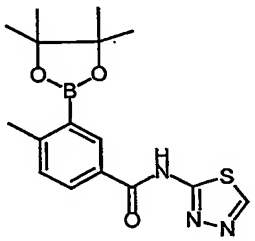
Intermediate 19: N-(3-Methoxy-phenyl)-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide



4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Intermediate 4) (2g) was dissolved in DMF (20ml). To this was added 3-methoxyaniline (0.985g), DIPEA (4ml) and HATU (3.05g). The mixture was stirred for 18 h at room temp. The solvent was removed under vacuum and the residue was partitioned between ethyl acetate (250ml) and water (50ml). The organic layer was dried (magnesium sulphate) concentrated under vacuum and purified using a silica Biotage cartridge (90g) eluting with 1:4 ethyl acetate/cyclohexane to give the title compound as a white solid (2.06g).

NMR: δH [d6-DMSO] 10.20, (1H, s), 8.17, (1H, s), 7.94-7.91, (1H, dd), 7.45, (1H, s), 7.36-7.32, (2H, t), 7.25-7.21, (1H, t), 6.68-6.65, (1H, dd), 3.74, (3H, s), 2.53, (3H, s), 1.32, (12H, s).
LCMS: Rt 3.80min MH^+ 368.

Intermediate 20: 4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-([1,3,4]thiadiazol-2-yl)-benzamide

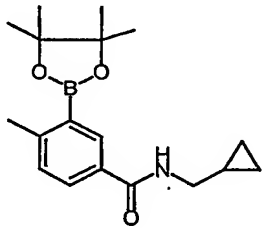


4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Intermediate 4) (2.0g), DIPEA (4ml) and HATU (3.05g) were dissolved in DMF (20ml) and stirred at room temp for 15min. 2-Aminothiadiazole (810mg) was added and the mixture was stirred at room temp for 18h. The solvent was evaporated under vacuum and the residue was partitioned between ethyl acetate (250ml) and hydrochloric acid (2N,

150ml). The aqueous phase was extracted with ethyl acetate (2 x 250ml). The combined organic extracts were dried (magnesium sulphate) and the solvent was removed under vacuum. The residue was absorbed onto silica and purified by flash column chromatography eluting with cyclohexane/ethyl acetate (4:1 then 1:1) to give the title compound (0.95g).

NMR: δH [d6-DMSO] 13.08,(1H, b), 9.22,(1H, s), 8.35,(1H, d), 8.11,(1H, dd), 7.38,(1H, d), 2.55,(3H, s), 1.34,(12H, s).
LCMS: Rt 3.34min, MH^+ 346.

Intermediate 21: N-Cyclopropylmethyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide



4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzoic acid (Intermediate 4) (2.0g) DIPEA (4ml) and HATU (3.05g) were dissolved in DMF (20ml) and stirred at room temp for 15min. Cyclopropylmethylamine (568mg) was added and the mixture was stirred at room temp for 18h. The solvent was removed under vacuum and the residue was partitioned between ethyl acetate (250ml) and water (50ml). The organic phase was washed with hydrochloric acid (2N, 50ml) and aqueous sodium bicarbonate (1M, 50ml) dried (magnesium sulphate) and concentrated under vacuum. The residue was absorbed onto silica and purified by flash column chromatography eluting with cyclohexane / ethyl acetate (4:1) to give the title compound (1.73g).

NMR: δH [d6-DMSO] 8.54,(1H, t), 8.11,(1H, d), 7.82,(1H, dd), 7.26,(1H, d), 3.12,(2H, t), 1.32,(12H, s), 1.03,(1H, m), 0.42,(2H, m), 0.22,(2H, m).
LCMS: Rt 3.47min, MH^+ 316.

General Method A

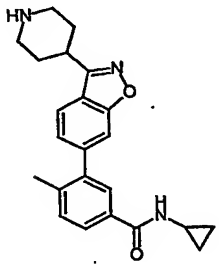
The halide (30μmoles) was dissolved in DME or DMF (0.4 - 0.5ml). The boronate ester (30μmoles in 0.2ml DME or DMF), sodium carbonate (10% aqueous solution, 0.25ml) and
(A) tetrakis (triphenylphosphine) palladium (3.5μmoles in 0.1ml DME) or
(B) FibreCat™ 1001 (12mg)
were added and the mixture was heated under nitrogen at 80° for 18h. The reaction mixture was

(A) filtered through silica (100mg) and washed with methanol
(B) filtered through Celite and washed with DME or DMF.
The solvent was evaporated and the residue was dissolved in DMSO (0.25ml) and purified by preparative mass-directed LC-MS.

General Method B

A solution of N-cyclopropyl-3-(1H-indazol-5-yl)-4-methylbenzamide (Example 17, 30mg) in dichloromethane (2ml) was added to the sulfonyl chloride (0.11mmol). Pyridine (50μmol) was added and the solution was stirred at 20° for 18h (if a solution is not generated a substantial quantity of the 2-substituted product is formed). The solvent was evaporated and the residue was purified by column chromatography on silica eluting with cyclohexane:ethyl acetate (4:1 to 1:1).

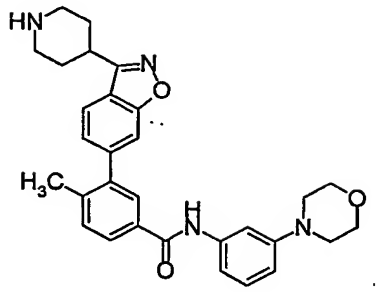
Example 1: *N*-Cyclopropyl-4-methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide



Example 1 was prepared by General Method A using 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole and Intermediate 5.

NMR: δH [d6-DMSO] 8.43 (1H, s), 8.08 (1H, d), 7.75 (3H, m), 7.43(2H, t), 3.6 (1H, m), 3.4(2H, m) 3.12 (2H, m), 2.85 (2H, m), 2.3 (3H, s), 2.2 (2H, m), 2.1 (2H, m), 0.67 (2H, m), 0.56 (2H, m).
LCMS: Rt 2.31min, MH^+376.

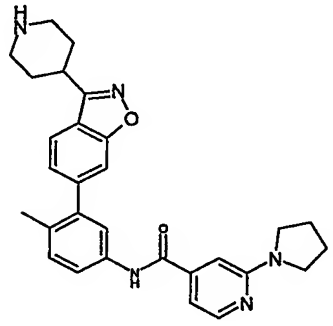
Example 2: 4-Methyl-*N*-(3-morpholin-4-ylphenyl)-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide



Example 2 was prepared by General Method A using 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole and Intermediate 10.

NMR: δH [d6-DMSO] 10.09 (1H, s), 8.09 (1H, d), 7.94 (1H, dd), 7.91 (1H, brs), 7.82 (1H, brs), 7.51 (1H, d), 7.47 (1H, d), 7.39 (1h, brs), 7.29 (1H, brd), 7.19 (1H, t), 6.70 (1H, dd), 3.74 (4H, apparent t), 3.48 (1H, brm), 3.29 (2H, brd), 3.09 (4H, apparent t), 2.95 (2H, brt), 2.34 (3H, s), 2.15 (2H, brd), 2.01 (2H, brt).
LCMS: Rt 2.56min, MH^+497.

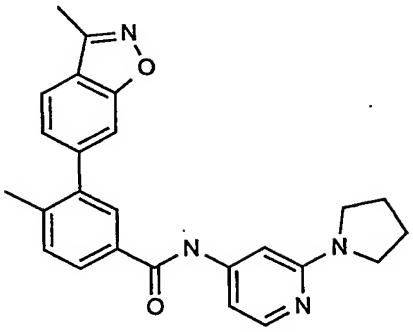
Example 3: *N*-[4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)phenyl]-2-pyrrolidin-1-ylisonicotinamide



Example 3 was prepared by General Method A using 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole and Intermediate 13.

NMR: δH [d6-DMSO] 10.3 (1H, s), 8.4 (1H, s), 8.2 (1H, d), 8.05 (1H,d), 7.75 (3H, m), 7.4(1H, d), 7.3 (1H, d), 6.95(1H, d), 6.85 (1H, s), 3.45 (4H, m), 3.2 (2H, d), 2.9(2H, t), 2.25 (3H, s), 2.1(2H, d), 1.95 (4H, m).
LCMS: Rt 2.26min, MH^+482.

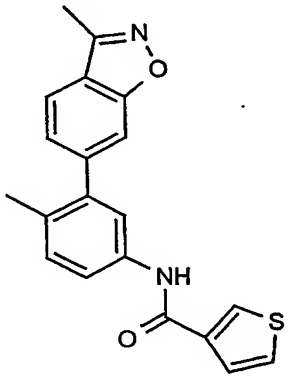
Example 4: N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)phenyl]-2-pyrrolidin-1-ylisonicotinamide



A mixture of 6-bromo-3-methyl-1,2-benzisoxazole (11mg), N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-pyrrolidin-1-yl-isonicotinamide (Intermediate 13, 15mg) and aqueous sodium carbonate (0.5M, 0.25ml) in anhydrous DME (1ml) was degassed then stirred under nitrogen. A solution of tetrakis(triphenylphosphine)palladium(0) (2.5mg) in DME (0.25ml) was added and the mixture was stirred at 80° for 16h. The solvent was removed under vacuum and the residue was partitioned between dichloromethane and water. The organic layer was separated using a hydrophobic filter, the solvent was evaporated and the residue was purified by column chromatography on silica, eluting with a cyclohexane-ethyl acetate gradient to give the title compound as an oil (5.6mg).

NMR δH [d6-DMSO, 600MHz] 10.3 (1H, br.s), 8.18 (1H, d), 7.93 (1H, d), 7.74 (1H, dd), 7.71 (1H, d), 7.67 (1H, s), 7.37 (1H, d), 7.37 (1H, d), 6.97 (1H, d), 6.86 (1H, s), 3.43 (4H, br.t), 2.60 (3H, s), 2.22 (3H, s), 1.96 (4H, br.t).
LC-MS: Rt 2.91min, MH+ 413.

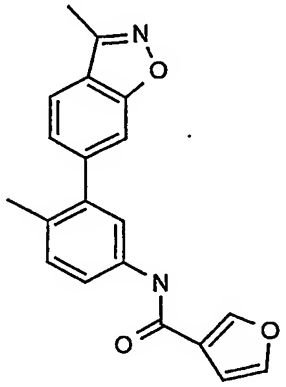
Example 5: N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)phenyl]thiophene-3-carboxamide



Example 5 was prepared in a similar manner to Example 4 using 6-bromo-3-methyl-1,2-benzisoxazole (11mg) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-thiopheneamide (Intermediate 15, 17mg) to give an oil (8.5mg).

NMR δH [d6-DMSO, 600MHz] 10.06 (1H, br.s), 8.32 (1H, dd), 7.93 (1H, d), 7.73 (1H, dd), 7.69 (1H, d), 7.67 (1H, br.s) 7.64 (1H, dd), 7.62 (1H, dd), 7.37 (1H, dd), 7.31 (1H, d), 2.60 (3H, s), 2.21 (3H, s).
LC-MS: Rt 3.51min, MH+ 349.

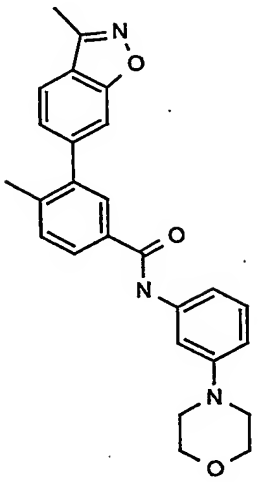
Example 6: N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)phenyl]-3-furamide



Example 6 was prepared in a similar manner to Example 4 using 6-bromo-3-methyl-1,2-benzisoxazole (11mg) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-furamide (Intermediate 17, 16mg) to give the title compound as an oil (8.6mg).

LC-MS: Rt 3.39, MH+ 333.

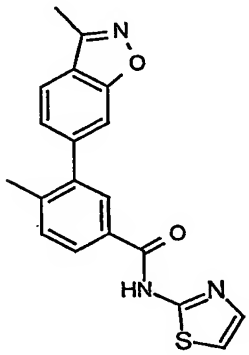
Example 7: 4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)-N-(3-morpholin-4-ylphenyl)benzamide



Example 7 was prepared in a similar manner to Example 4 using 6-bromo-3-methyl-1,2-benzisoxazole (11mg) and 4-methyl-N-(3-morpholin-4-yl-phenyl)-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 9, 21mg) to give the title compound as an oil (9.6mg).

NMR δH [d6-DMSO, 600MHz] 10.07 (1H, br.s), 7.96-7.88 (3H, m), 7.76 (1H, S), 7.50 (1H, d), 7.46 (1H, d), 7.38 (1H, br.s), 7.28 (1H, br.d), 7.18 (1H, t), 6.70 (1H, dd), 3.74 (4H, m), 2.60 (3H, s), 2.32 (3H, s).
LC-MS: Rt 3.47min, MH+ 428.

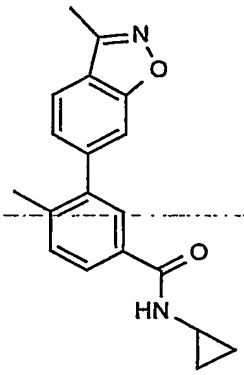
Example 8: 4-Methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)-N-(1,3-thiazol-2-yl)benzamide



Example 8 was prepared in a similar manner to Example 4 using 6-bromo-3-methyl-1,2-benzisoxazole (11mg) and N-(thiazol-2-yl)-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 18, 17mg) followed by purification *via* mass directed autoprep to give the title compound as an oil (1.3mg).

LC-MS: Rt 3.45min, MH+ 350.

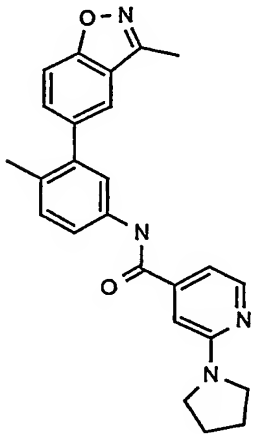
Example 9: N-Cyclopropyl-4-methyl-3-(3-methyl-1,2-benzisoxazol-6-yl)benzamide



Example 9 was prepared in a similar manner to Example 4 using 6-bromo-3-methyl-1,2-benzisoxazole (11mg) and N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 5, 15mg) to give the title compound as an oil (8.5mg).

NMR δH [d6-DMSO, 600MHz] 8.43 (1H, br.d), 7.92 (1H, d), 7.78 (1H, dd), 7.74 (1H, d), 7.70 (1H, s), 7.42-7.37 (2H, 2xd), 2.85 (1H, m), 2.60 (3H, s), 2.27 (3H, s), 0.67 (2H, m), 0.55 (2H, m).
LC-MS: Rt 3.19min, MH+ 307.

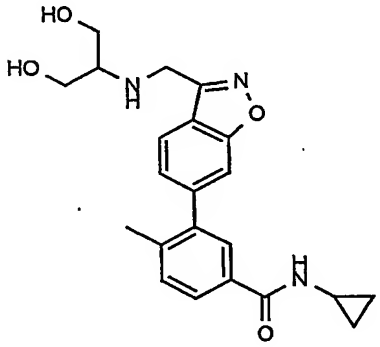
Example 10: N-[4-Methyl-3-(3-methyl-1,2-benzisoxazol-5-yl)phenyl]-2-pyrrolidin-1-ylisonicotinamide



Example 10 was prepared in a similar manner to Example 4 using 5-bromo-3-methyl-1,2-benzisoxazole (11mg) and N-[4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-2-pyrrolidin-1-yl-isonicotinamide (Intermediate 13, 16mg) to give the title compound as an oil (6.6).

LC-MS: Rt 2.91min, MH+ 413.

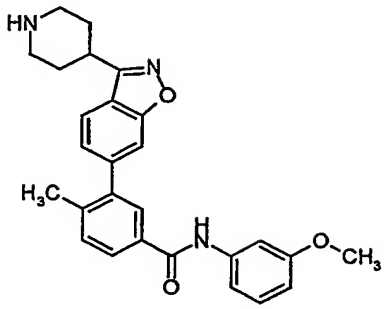
Example 11: N-Cyclopropyl-3-[3-({[2-hydroxy-1-(hydroxymethyl)ethyl]amino}methyl)-1,2-benzisoxazol-6-yl]-4-methylbenzamide



A mixture of 2-[(6-bromo-1,2-benzisoxazol-3-yl)methyl]amino-1,3-propanediol (Intermediate 2, 8mg), N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 5, 10mg) aqueous sodium carbonate (1M, 0.1ml) and tetrakis(triphenylphosphine)palladium(0) (1mg) in 2-propanol (0.2ml) was stirred at 80° under nitrogen for 18h. The solvent was evaporated and the residue was purified on a Varian Bond-Elut SPE cartridge (silica, 500mg) using a dichloromethane-methanol elution gradient (19:1 to 9:1) to give the title compound as an oil (3mg).

NMR δH [d6-DMSO] 8.43 (1H, br.d), 8.08 (1H, d), 7.80 (1H, dd), 7.75 (1H, d), 7.73 (1H, br.s), 7.40 (2H, 2xd), 4.48 (2H, br.t), 4.24 (2H, s), 3.42 (4H, m), 2.85 (1H, m), 2.61 (1H, m), 2.28 (3H, s), 0.72-0.53 (4H, m).
LC-MS: Rt 2.15min, MH+ 396.

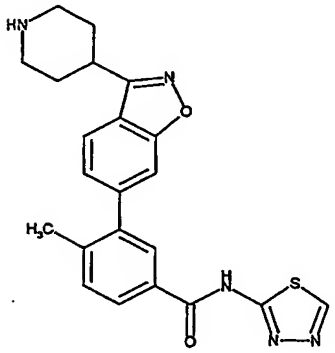
Example 12: N-(3-Methoxyphenyl)-4-methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide



N-(3-Methoxyphenyl)-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 19, 54mg), DME (3ml), aqueous sodium carbonate (1M, 2ml), tetrakis (triphenylphosphine) palladium (20mg) and 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole (44mg) were heated together at 80°C under nitrogen for 18h. The solvent was evaporated and the residue was purified by column chromatography on silica (10g) eluting with dichloromethane:ethanol:ammonia (40:8:1) to give the title compound (37mg).

NMR: δH[d6-DMSO] 8.05 (1H, d), 7.88-7.97 (2H, m), 7.79 (1H, s), 7.50 (1H, d), 7.42-7.47 (2H, m), 7.36 (1H, br d), 7.23 (1H, dd), 6.67 (1H, dd), 3.09-3.14 (5H, m), 2.76 (2H, m), 2.32 (3H, s), 1.99 (2H, m), 1.83 (2H, m).
LCMS: Rt 2.66min, MH^+ 442.

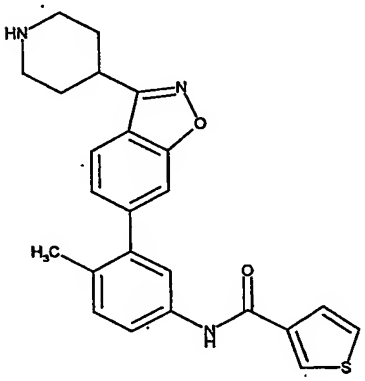
Example 13: 4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)-N-(1,3,4-thiadiazol-2-yl)benzamide



4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(thiadiazol-2-yl)-benzamide (Intermediate 20, 50.7mg), DME (3ml), aqueous sodium carbonate (1M, 2ml), tetrakis (triphenylphosphine) palladium (20mg) and 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole (44mg) were heated together at 80°C under nitrogen for 18h. The mixture was evaporated and the residue was purified by column chromatography on silica (10g) eluting with cyclohexane:ethyl acetate (8:1 to 1:1) followed by dichloromethane:ethanol:ammonia (20:8:1) to give the title compound (30.1mg).

NMR: δH[d6-DMSO] 8.95 (1H, s), 8.01-8.09 (4H, m), 7.80 (1H, s), 7.47 (1H, d), 7.45 (1H, d), 3.25-3.47 (3H, m), 2.97 (2H, dd), 2.32 (3H, s), 2.14 (2H, m), 1.97 (2H, m).
LCMS: Rt 2.44min, MH^+ 420.

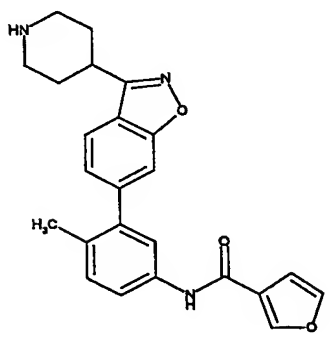
Example 14: N-[4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)phenyl]thiophene-3-carboxamide



N-[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]thiophene-3-amide (Intermediate 15, 50mg), DMF (1.5ml), aqueous sodium carbonate (1M, 0.75ml), tetrakis (triphenylphosphine) palladium (7.5mg) and 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole (41mg) were heated together at 80°C under nitrogen for 18h. The solvent was evaporated, and the residue was purified by column chromatography on silica (10g) eluting with dichloromethane:ethanol:ammonia (100:8:1) to give the title compound (36.8mg).

NMR: δH[d6-DMSO] 10.07 (1H, d), 8.32 (1H, s), 8.00 (1H, dd), 7.59-7.74 (4H, m), 7.35 (1H, d), 7.29 (1H, dd), 6.94 (1H, d), 3.02 (2H, m), 2.66 (2H, m), 2.20 (3H, s), 1.96 (1H, m), 1.78 (2H, m), 1.50 (1H, m).
LCMS: Rt 2.71min, MH^+ 418.

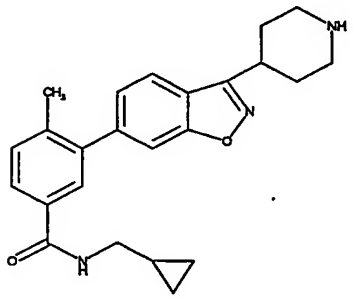
Example 15: N-[4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)phenyl]-3-furamide



N-[4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-phenyl]-3-furamide (Intermediate 17, 47mg), DMF (1.5ml), aqueous sodium carbonate (1M, 0.75ml), tetrakis (triphenylphosphine) palladium (7.5mg) and 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole (41mg) were heated together at 80°C under nitrogen for 18h. The solvent was evaporated and the residue was purified by column chromatography on silica (10g) eluting with dichloromethane:ethanol:ammonia (100:8:1) to give the title compound (37.8mg).

NMR: δH[d6-DMSO] 9.93 (1H, d), 8.35 (1H, s), 8.00 (1H, dd), 7.78 (1H, s), 7.61-7.69 (2H, m), 7.35 (1H, d), 7.28 (1H, dd), 6.98 (1H, s), 3.02 (2H, m), 2.65 (2H, m), 2.21 (3H, s), 1.96 (1H, m), 1.77 (2H, m), 1.49 (1H, m).
LCMS: Rt 2.55min, MH^+ 402.

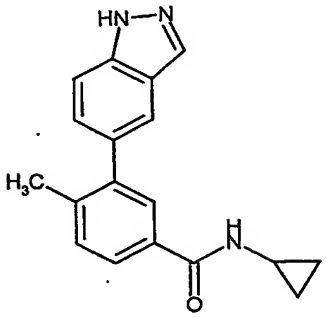
Example 16: N-(Cyclopropylmethyl)-4-methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)benzamide



N-Cyclopropylmethyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 21, 100mg), DME (5ml), aqueous sodium carbonate (1M, 3ml), tetrakis (triphenylphosphine) palladium (0) (37mg) and 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole (76mg) were heated together at 80°C under nitrogen for 18h. The solvent was evaporated and the residue was purified by column chromatography on silica (10g) eluting with dichloromethane:ethanol:ammonia (100:8:1 to 70:8:1) to give the title compound (53mg).

NMR: δH[d6-DMSO] 8.56 (1H, t), 8.03 (1H, d), 7.81 (1H, dd), 7.78 (1H, s), 7.74 (1H, s), 7.42 (1H, d), 7.38 (1H, d), 3.12 (2H, t), 3.05 (2H, m), 2.68 (2H, m), 2.29 (3H, s), 1.95 (2H, m), 1.78 (2H, m), 1.00 (1H, m), 0.41 (2H, m), 0.20 (2H, m).
LCMS: Rt 2.56min, MH^+ 390.

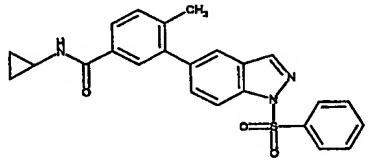
Example 17: N-Cyclopropyl-3-(1H-indazol-5-yl)-4-methylbenzamide



To a solution of tert-butyl 5-bromo-1H-indazole-1-carboxylate (Intermediate 3, 2.0g) and N-cyclopropyl-4-methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-benzamide (Intermediate 5, 2.04g) in DME (125ml) was added tetrakis (triphenylphosphine) palladium (0.78g) and aqueous sodium carbonate (1M, 80ml). The mixture was heated at reflux under nitrogen for 16h. The solvent was evaporated and the residue was purified by column chromatography on silica, eluting with cyclohexane:ethyl acetate (2:1 to 1:1) to give the title compound (1.38g).

NMR: δH [$CDCl_3$] 8.10 (1H, s), 7.31-7.68 (7H, m), 6.26 (1H, br s), 2.89 (1H, m), 2.29 (3H, s), 0.86 (2H, m), 0.60 (2H, m).
LCMS: Rt 2.82min, MH^+ 292.

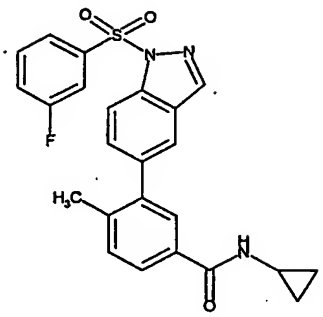
Example 18: N-Cyclopropyl-4-methyl-3-[1-(phenylsulfonyl)-1H-indazol-5-yl]benzamide



Example 18 was prepared by General Method B using benzenesulfonyl chloride to give the title compound (10.4mg).

NMR: δH[d6-DMSO] 8.58 (1H, d), 8.38 (1H, d), 8.19 (1H, d), 7.97 (2H, d), 7.85 (1H, s), 7.62-7.77 (6H, m), 7.39 (1H, d), 2.82 (1H, m), 2.24 (3H, s), 0.65 (2H, m), 0.53 (2H, m).
LCMS: Rt 3.37min, MH^+ 432.

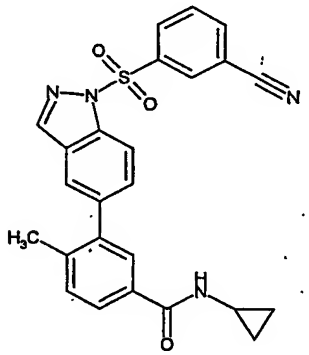
Example 19: N-Cyclopropyl-3-{1-[(3-fluorophenyl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide



Example 19 was prepared by General Method B using 3-fluorobenzenesulfonyl chloride to give the title compound (19.2mg).

NMR: δH[d6-DMSO] 8.62 (1H, s), 8.38 (1H, d), 8.20 (1H, d), 7.86 (1H, s), 7.60-7.84 (7H, m), 7.39 (1H, d), 2.82 (1H, m), 2.24 (3H, s), 0.65 (2H, m), 0.53 (2H, m).
LCMS: Rt 3.44min, MH^+ 450.

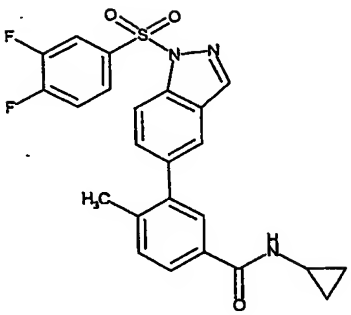
Example 20: 3-{1-[(3-Cyanophenyl)sulfonyl]-1H-indazol-5-yl}-N-cyclopropyl-4-methylbenzamide



Example 20 was prepared by General Method B using 3-cyanobenzenesulfonyl chloride to give the title compound (14.5mg).

NMR: δH[d6-DMSO] 8.64 (1H, s), 8.51 (1H, s), 8.39 (1H, d), 8.27 (1H, d), 8.21-8.24 (2H, m), 7.87 (1H, s), 7.83 (1H, dd), 7.76 (1H, d), 7.68-7.72 (2H, m), 7.39 (1H, d), 2.82 (1H, m), 2.24 (3H, s), 0.65 (2H, m), 0.51 (2H, m).
LCMS: Rt 3.34min, MH^+ 457.

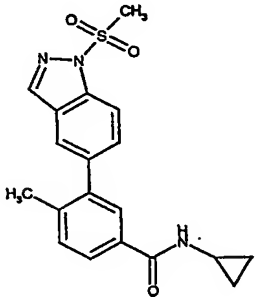
Example 21: N-Cyclopropyl-3-{1-[(3,4-difluorophenyl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide



Example 21 was prepared by General Method B using 3,4-difluorobenzenesulfonyl chloride to give the title compound (15.6mg).

NMR: δH[d6-DMSO] 8.63 (1H, s), 8.40 (1H, br d), 8.21 (1H, d), 8.16 (1H, td), 7.85-7.90 (2H, m), 7.65-7.80 (4H, m), 7.40 (1H, d), 2.82 (1H, m), 2.25 (3H, s), 0.67 (2H, m), 0.54 (2H, m).
LCMS: Rt 3.49min, MH^+ 468.

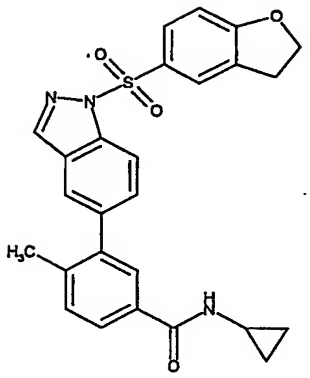
Example 22: N-Cyclopropyl-4-methyl-3-[1-(methylsulfonyl)-1H-indazol-5-yl]benzamide



Example 22 was prepared by General Method B using methanesulfonyl chloride to give the title compound (6.9mg).

NMR: δH[d6-DMSO] 8.64 (1H, s), 8.42 (1H, d), 8.03 (1H, d), 7.91 (1H, s), 7.76 (1H, d), 7.73 (1H, s), 7.66 (1H, dd), 7.40 (1H, d), 3.50 (3H, s), 2.84 (1H, m), 2.28 (3H, s), 0.67 (2H, m), 0.55 (2H, m).
LCMS: Rt 2.97min, MH^+ 370.

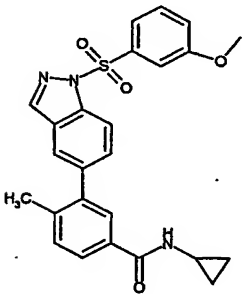
Example 23: N-Cyclopropyl-3-[1-(2,3-dihydro-1-benzofuran-5-ylsulfonyl)-1H-indazol-5-yl]-4-methylbenzamide



Example 23 was prepared by General Method B using 2,3-dihydro-1-benzofuran-5-sulfonyl chloride to give the title compound (9.2mg).

NMR: δH[d6-DMSO] 8.54 (1H, s), 8.39 (1H, d), 8.17 (1H, d), 7.82-7.86 (2H, m), 7.74-7.77 (2H, m), 7.70 (1H, br s), 7.66 (1H, dd), 7.39 (1H, d), 6.93 (1H, d), 4.62 (2H, dd), 3.21 (2H, dd), 2.83 (1H, m), 2.25 (3H, s), 0.66 (2H, m), 0.54 (2H, m).
MS: e/z+ 474.

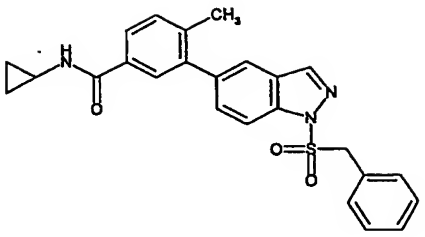
Example 24: N-Cyclopropyl-3-{1-[(3-methoxyphenyl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide



Example 24 was prepared by General Method B using 3-methoxyphenylsulfonyl chloride to give the title compound (11.0mg).

NMR: δH[d6-DMSO] 8.59 (1H, s), 8.39 (1H, d), 8.19 (1H, d), 7.85 (1H, s), 7.76 (1H, d), 7.65-7.73 (2H, m), 7.49-7.54 (2H, m), 7.37-7.41 (2H, m), 7.30 (1H, d), 3.78 (3H, s), 2.82 (1H, m), 2.24 (3H, s), 0.66 (2H, m), 0.53 (2H, m).
LCMS: Rt 3.42min, MH^+ 462.

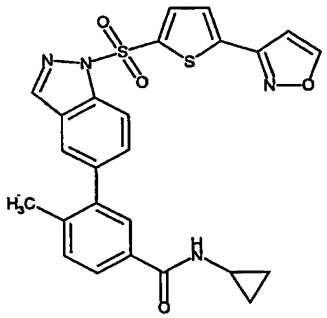
Example 25: 3-[1-(Benzylsulfonyl)-1H-indazol-5-yl]-N-cyclopropyl-4-methylbenzamide



Example 25 was prepared by General Method B using benzylsulfonyl chloride to give the title compound (16.4mg).

NMR: δH[d6-DMSO] 8.64 (1H, s), 8.41 (1H, d), 7.80 (1H, s), 7.75 (1H, dd), 7.67 (1H, d), 7.51 (1H, d), 7.37 (1H, dd), 7.18 (1H, dd), 7.12 (2H, dd), 7.00 (2H, d), 5.02 (3H, s), 2.83 (1H, m), 2.21 (3H, s), 0.67 (2H, m), 0.54 (2H, m).
LCMS: Rt 3.34min, MH^+ 446.

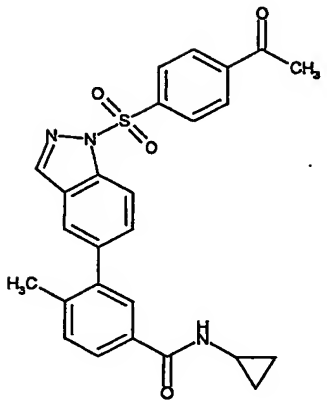
Example 26: N-Cyclopropyl-3-{1-[(5-isoxazol-3-ylthien-2-yl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide



Example 26 was prepared by General Method B using 5-isoxazol-3-ylthiophene-2-sulfonyl chloride to give the title compound (3.5mg).

NMR: δH[d6-DMSO] 8.73 (1H, s), 8.70 (1H, s), 8.39 (1H, d), 8.16 (1H, d), 8.03 (1H, d), 7.90 (1H, s), 7.69-7.79 (4H, m), 7.39 (1H, d), 7.16 (1H, d), 2.83 (1H, m), 2.25 (3H, s), 0.66 (2H, m), 0.52 (2H, m).
LCMS: Rt 3.46min, MH^+ 505.

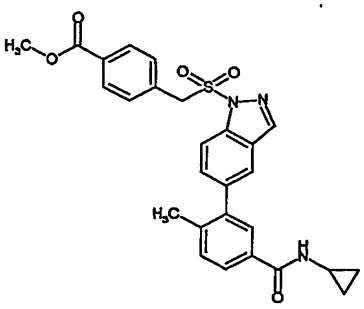
Example 27: 3-{1-[(4-Acetylphenyl)sulfonyl]-1H-indazol-5-yl}-N-cyclopropyl-4-methylbenzamide



Example 27 was prepared by General Method B using 4-acetylphenylsulfonyl chloride to give the title compound (3.6mg).

NMR: δH[d6-DMSO] 8.62 (1H, s), 8.38 (1H, d), 8.21 (1H, d), 8.10 (4H, m), 7.86 (1H, s), 7.76 (1H, dd), 7.69-7.71 (2H, m), 7.39 (1H, d), 2.83 (1H, m), 2.57 (3H, s), 2.24 (3H, s), 0.66 (2H, m), 0.52 (2H, m).
LCMS: Rt 3.32min, MH^+ 474.

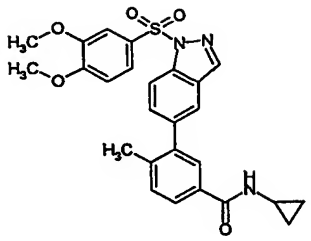
Example 28: Methyl 4-{[(5-{5-[(cyclopropylamino)carbonyl]-2-methylphenyl}-1H-indazol-1-yl)sulfonyl]methyl}benzoate



Example 28 was prepared by General Method B using methyl 4-[(chlorosulfonyl)methyl]benzoate to give the title compound (7.8mg).

NMR: δH[d6-DMSO] 8.64 (1H, s), 8.39 (1H, d), 7.78 (1H, s), 7.74 (1H, d), 7.66 (2H, d), 7.64 (1H, s), 7.45 (1H, d), 7.37 (1H, d), 7.31 (1H, d), 7.11 (2H, d), 5.17 (2H, s), 3.76 (3H, s), 2.83 (1H, m), 2.13 (3H, s), 0.67 (2H, m), 0.54 (2H, m).
LCMS: Rt 3.38min, MH^+ 504.

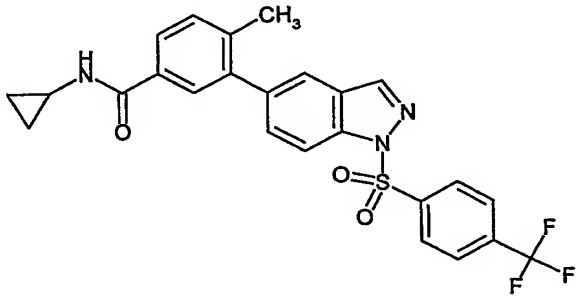
Example 29: N-Cyclopropyl-3-{1-[(3,4-dimethoxyphenyl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide



Example 29 was prepared by General Method B using 3,4-dimethoxybenzenesulfonyl chloride to give the title compound (4.2mg).

NMR: δH[d6-DMSO] 8.56 (1H, s), 8.39 (1H, d), 8.20 (1H, d), 7.84 (1H, s), 7.75 (1H, d), 7.70 (1H, s), 7.66 (1H, d), 7.57 (1H, dd), 7.39 (1H, d), 7.35 (1H, d), 7.14 (1H, d), 3.80 (3H, s), 3.77 (3H, s), 2.83 (1H, m), 2.24 (3H, s), 0.65 (2H, m), 0.53 (2H, m).
LCMS: Rt 3.29min, MH^+ 492.

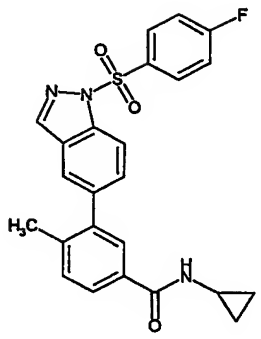
Example 30: N-Cyclopropyl-4-methyl-3-(1-{[4-(trifluoromethyl)phenyl]sulfonyl}-1H-indazol-5-yl)benzamide



Example 30 was prepared by General Method B using 4-(trifluoromethyl)benzenesulfonyl chloride to give the title compound (13.3mg).

NMR: δH[d6-DMSO 8.64 (1H, s), 8.39 (1H, d), 8.17-8.23 (3H, m), 8.02 (2H, d), 7.87 (1H, s), 7.76 (1H, d), 7.71 (1H, d), 7.70 (1H, s), 7.39 (1H, d), 2.83 (1H, m), 2.24 (3H, s), 0.65 (2H, m), 0.53 (2H, m).
LCMS: Rt 3.61min, MH^+ 500.

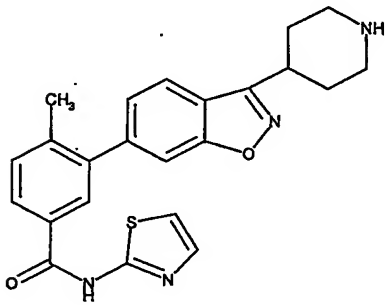
Example 31: N-Cyclopropyl-3-{1-[(4-fluorophenyl)sulfonyl]-1H-indazol-5-yl}-4-methylbenzamide



Example 31 was prepared by General Method B using 4-fluorobenzenesulfonyl chloride to give the title compound (13.3mg).

NMR: δH[d6-DMSO] 8.39 (1H, s), 8.25 (1H, d), 8.06 (2H, dd), 7.76 (1H, s), 7.71 (1H, d), 7.66 (1H, s), 7.62 (1H, d), 7.38 (1H, d), 7.29 (2H, dd), 2.82 (1H, m), 2.27 (3H, s), 0.78 (2H, m), 0.61 (2H, m).
LCMS: Rt 3.41min, MH^+ 450.

Example 32: 4-Methyl-3-(3-piperidin-4-yl-1,2-benzisoxazol-6-yl)-*N*-(1,3-thiazol-2-yl)benzamide



4-Methyl-3-(4,4,5,5-tetramethyl-[1,3,2]dioxaborolan-2-yl)-N-(thiazol-2-yl)-benzamide (Intermediate 18, 50mg), DME (3ml), aqueous sodium carbonate (1M, 2ml), tetrakis(triphenylphosphine)palladium (20mg) and 6-bromo-3-piperidin-4-yl-1,2-benzisoxazole (44mg, 147μmol) were heated together at 80°C under nitrogen for 18h. The solvent was evaporated, and the residue was purified by column chromatography on silica (10g) eluting with dichloromethane:ethanol:ammonia (100:8:1) to give the title compound (43mg).

NMR: δH[d6-DMSO] 8.00-8.09 (3H, m), 7.81 (1H, s), 7.44-7.52 (3H, m), 7.19 (1H, d), 3.08 (2H, m), 2.69 (2H, m), 2.34 (3H, s), 1.98 (2H, m), 1.80 (2H, m).
LCMS: Rt 2.53min, MH^+ 419.

Abbreviations

DIPEA	N,N-Diisopropylethylamine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulphoxide
HATU	O-(7-Azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
$PdCl_2dppf$	[1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium (II) complex with dichloromethane (1:1)
Rt	Retention Time
SPE	Solid phase extraction

BIOLOGICAL EXAMPLES

The activity of compounds of formula (I) as p38 inhibitors may be determined by the following *in vitro* assays:

Fluorescence anisotropy kinase binding assay

The kinase enzyme, fluorescent ligand and a variable concentration of test compound are incubated together to reach thermodynamic equilibrium under conditions such that in the absence of test compound the fluorescent ligand is significantly (>50%) enzyme bound and in the presence of a sufficient concentration (>10x K_i) of a potent inhibitor the anisotropy of the unbound fluorescent ligand is measurably different from the bound value.

The concentration of kinase enzyme should preferably be $\geq 1 \times K_f$. The concentration of fluorescent ligand required will depend on the instrumentation used, and the fluorescent and physicochemical properties. The concentration used must be lower than the concentration of kinase enzyme, and preferably less than half the kinase enzyme concentration. A typical protocol is:

All components dissolved in Buffer of final composition 62.5 mM HEPES, pH 7.5, 1.25 mM CHAPS, 1.25 mM DTT, 12.5 mM $MgCl_2$ 3.3% DMSO.

p38 Enzyme concentration: 12 nM

Fluorescent ligand concentration: 5 nM

Test compound concentration: 0.1 nM - 100 uM

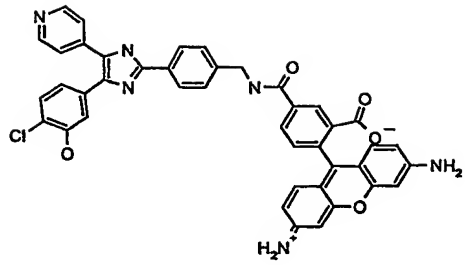
Components incubated in 30 ul final volume in NUNC 384 well black microtitre plate until equilibrium reached (5-30 mins)

Fluorescence anisotropy read in LJL Acquest.

Definitions: K_i = dissociation constant for inhibitor binding

K_f = dissociation constant for fluorescent ligand binding

The fluorescent ligand is the following compound:



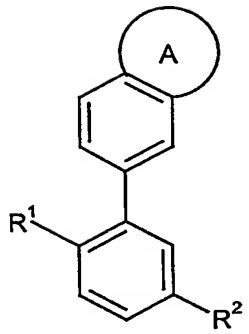
which is derived from 5-[2-(4-aminomethylphenyl)-5-pyridin-4-yl-1H-imidazol-4-yl]-2-chlorophenol and rhodamine green.

Results

The compounds described in the Examples were tested as described above and had IC_{50} values of <10 μM.

Claims:

1. A compound of formula (I):



(I)

wherein

A is a fused 5-membered heteroaryl ring optionally substituted by up to two substituents independently selected from C_{1-6}alkyl, -$(CH_2)_m$-C_{3-7}cycloalkyl, halogen, cyano, trifluoromethyl, -$(CH_2)_m$$OR^3$, -$(CH_2)_m$$NR^3R^4$, -$(CH_2)_m$$CONR^3R^4$, -$(CH_2)_m$$NHCOR^3$, -$(CH_2)_m$$SO_2NR^3R^4$, -$(CH_2)_m$$NHSO_2R^3$, -$(CH_2)_m$$SO_2(CH_2)_nR^5$, a 5- or 6-membered heterocyclyl ring containing nitrogen optionally substituted by C_{1-2}alkyl and a 5-membered heteroaryl ring optionally substituted by C_{1-2}alkyl;

R^1 is selected from methyl and chloro;

R^2 is selected from -NH-CO-R^6 and -CO-NH-$(CH_2)_q$-R^7;

R^3 is selected from hydrogen, C_{1-6}alkyl optionally substituted by up to two OH groups, -$(CH_2)_m$-C_{3-7}cycloalkyl, -$(CH_2)_m$phenyl optionally substituted by R^8 and/or R^9 and -$(CH_2)_m$heteroaryl optionally substituted by R^8 and/or R^9

R^4 is selected from hydrogen and C_{1-6}alkyl, or

R^3 and R^4, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

R^5 is selected from C_{1-6}alkyl, C_{3-7}cycloalkyl, heteroaryl optionally substituted by R^8 and/or R^9, and phenyl optionally substituted by R^8 and/or R^9;

R^6 is selected from hydrogen, C_{1-6}alkyl, -$(CH_2)_q$-C_{3-7}cycloalkyl, trifluoromethyl, -$(CH_2)_r$heteroaryl optionally substituted by R^{11} and/or R^{12}, and -$(CH_2)_r$phenyl optionally substituted by R^{11} and/or R^{12};

R^7 is selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, $CONHR^{13}$, phenyl optionally substituted by R^{11} and/or R^{12}, and heteroaryl optionally substituted by R^{11} and/or R^{12};

R^8 and R^9 are each independently selected from halogen, cyano, trifluoromethyl, C_{1-6}alkyl, C_{1-6}alkoxy, COR^{15} , CO_2R^{15}, and heteroaryl, or

R^8 and R^9 are linked to form a fused 5-membered heterocyclyl ring containing one heteroatom selected from oxygen, sulphur and N-R^{10};

R^{10} is selected from hydrogen and methyl;

R^{11} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, -$(CH_2)_q$-C_{3-7}cycloalkyl, -$CONR^{13}R^{14}$, -$NHCOR^{14}$, halogen, CN, -$(CH_2)_sNR^{16}R^{17}$, trifluoromethyl, phenyl optionally substituted by one or more R^{12} groups, and heteroaryl optionally substituted by one or more R^{12} groups;

R^{12} is selected from C_{1-6}alkyl, C_{1-6}alkoxy, halogen, trifluoromethyl, and -$(CH_2)_sNR^{16}R^{17}$;

R^{13} and R^{14} are each independently selected from hydrogen and C_{1-6}alkyl, or

R^{13} and R^{14}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10}, wherein the ring may be substituted by up to two C_{1-6}alkyl groups;

R^{15} is C_{1-6}alkyl;

R^{16} is selected from hydrogen, C_{1-6}alkyl and -$(CH_2)_q$-C_{3-7}cycloalkyl optionally substituted by C_{1-6}alkyl,

R^{17} is selected from hydrogen and C_{1-6}alkyl, or

R^{16} and R^{17}, together with the nitrogen atom to which they are bound, form a 5- or 6-membered heterocyclic ring optionally containing one additional heteroatom selected from oxygen, sulfur and N-R^{10};

m is selected from 0, 1, 2 and 3;

n is selected from 0, 1, 2 and 3;

q is selected from 0, 1 and 2;

r is selected from 0 and 1; and

s is selected from 0, 1, 2 and 3.

2. A compound according to claim 1 as defined in any one of Examples 1 to 32.

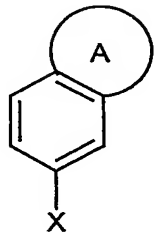
3. A pharmaceutical composition comprising a compound as claimed in claim 1 in admixture with one or more pharmaceutically acceptable carriers, diluents or excipients.

4. A method for treating a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase comprising administering to a patient in need thereof a compound as claimed in claim 1.

5. Use of a compound as claimed in claim 1 in the manufacture of a medicament for use in the treatment of a condition or disease state mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38 kinase.

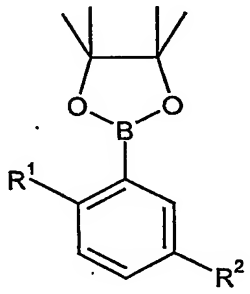
6. A process for preparing a compound of formula (I) as claimed in claim 1 which comprises

(a) reacting a compound of formula (II)



(II)

in which A is as hereinbefore defined and X is halogen,
with a compound of formula (III)



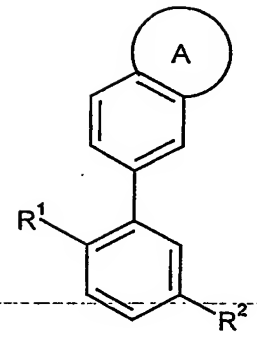
(III)

in which R^1 and R^2 are as hereinbefore defined,
in the presence of a catalyst, or

(b) final stage modification of one compound of formula (I) as defined in claim 1 to give another compound of formula (I) as defined in claim 1.

Abstract

Compounds of formula (I):



(I)

are inhibitors of p38 kinase and are useful in the treatment of conditions or disease states mediated by p38 kinase activity or mediated by cytokines produced by the activity of p38.

PCT Application
GB0303316